

Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza
Newark, NJ 07102
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff Sepracor Inc.

Of Counsel:

Joseph M. O'Malley, Jr.
Bruce M. Wexler
David M. Conca
Eric W. Dittmann
PAUL, HASTINGS, JANOFSKY & WALKER LLP
75 East 55th Street
New York, NY 10022
(212) 318-6000

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

SEPRACOR INC.,

Plaintiff,

v.

TEVA PHARMACEUTICALS USA, INC., TEVA
PHARMACEUTICAL INDUSTRIES, LTD.,
WOCKHARDT LTD., WOCKHARDT USA, INC.,
DR. REDDY'S LABORATORIES, LTD., DR.
REDDY'S LABORATORIES, INC., ROXANE
LABORATORIES, INC., COBALT
LABORATORIES INC., COBALT
PHARMACEUTICALS INC., GLENMARK
GENERICS INC., USA, GLENMARK
GENERICS, LTD., GLENMARK
PHARMACEUTICALS, LTD., ORCHID
HEALTHCARE (a Division of ORCHID
CHEMICALS & PHARMACEUTICALS, LTD.),
ORCHID CHEMICALS &
PHARMACEUTICALS, LTD., ORGENUS
PHARMA INC., LUPIN PHARMACEUTICALS,
INC., LUPIN LTD., SUN PHARMA GLOBAL
INC., SUN PHARMACEUTICAL INDUSTRIES
INC., SUN PHARMACEUTICAL INDUSTRIES
LTD., ALPHAPHARM PTY. LTD. and MYLAN,
INC.,

Defendants.

Civil Action No. _____

**COMPLAINT
FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiff Sepracor Inc. (“Sepracor”), for its Complaint against Defendants Teva Pharmaceuticals USA, Inc. (“Teva USA”), Teva Pharmaceutical Industries, Ltd. (“Teva Ltd.”), Wockhardt Ltd. (“Wockhardt Ltd.”), Wockhardt USA, Inc. (“Wockhardt USA”), Dr. Reddy’s Laboratories, Ltd. (“Reddy Ltd.”), Dr. Reddy’s Laboratories, Inc. (“Reddy Inc.”), Roxane Laboratories, Inc. (“Roxane”), Cobalt Laboratories Inc. (“Cobalt Labs”), Cobalt Pharmaceuticals Inc. (“Cobalt Pharma”), Glenmark Generics Inc., USA (“Glenmark USA”), Glenmark Generics, Ltd. (“Glenmark Ltd.”), Glenmark Pharmaceuticals, Ltd. (“Glenmark Pharma”), Orchid Healthcare (a Division of Orchid Chemicals & Pharmaceuticals, Ltd.), (“Orchid Healthcare”), Orchid Chemicals & Pharmaceuticals, Ltd. (“Orchid Ltd.”), Orgenus Pharma Inc. (“Orgenus”), Lupin Pharmaceuticals, Inc. (“Lupin Pharma”), Lupin Ltd. (“Lupin Ltd.”), Sun Pharma Global Inc. (“Sun Global”), Sun Pharmaceutical Industries Inc. (“Sun Pharma Inc.”), Sun Pharmaceutical Industries Ltd. (“Sun Pharma Ltd.”), Alphapharm Pty. Ltd. (“Alphapharm Ltd.”) and Mylan, Inc. (“Mylan Inc.”), (all defendants collectively, “Defendants”), hereby alleges as follows.

PARTIES

1.A. Plaintiff Sepracor is a Delaware corporation having its principal place of business at 84 Waterford Drive, Marlborough, MA 01752.

1.B. Upon information and belief, Defendant Teva USA is a Delaware corporation having a place of business located at 2 University Plaza, Hackensack, NJ 07601. Teva USA is a wholly owned subsidiary and agent of Defendant Teva Ltd. Upon information and belief, Defendant Teva USA has offices in New Jersey, is registered to do business in New Jersey and does business in this judicial district. Teva USA has previously consented to personal jurisdiction in this Court.

1.C. Upon information and belief, Defendant Teva Ltd. is an Israeli corporation having a place of business at 5 Basel Street, Petah Tiqva 49131, Israel. Upon information and belief, Defendant Teva Ltd., itself and through its wholly owned subsidiary and agent Defendant Teva USA, manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Teva Ltd. has previously consented to personal jurisdiction in this Court.

1.D. Defendant Teva USA and Defendant Teva Ltd. are collectively referred to as “Teva.”

1.E. Upon information and belief, Defendant Wockhardt Ltd. is an Indian corporation having a principal place of business at Wockhardt Towers, Bandra-Kurla Complex, Bandra (East), Mumbai, Maharashtra 400 051, India. Upon information and belief, Defendant Wockhardt Ltd. has an office in New Jersey and does business in this judicial district. Upon information and belief, Dr. Brij Khera, a New Jersey employee of Wockhardt Ltd., is authorized to negotiate access to Wockhardt Ltd.’s confidential information under Wockhardt Ltd.’s Offer of Confidential Access in this action, negotiated the terms of such access, and caused to be sent from New Jersey Wockhardt Ltd.’s confidential information that is the subject of Sepracor’s claims against Wockhardt Ltd. and Wockhardt USA in this action. Upon information and belief, Defendant Wockhardt Ltd., itself and through its agent Defendant Wockhardt USA, manufactures generic drugs for sale and use throughout the United States, including in this judicial district.

1.F. Upon information and belief, Defendant Wockhardt USA is a Delaware corporation having a place of business at 135 Route 202/206, Bedminster, New Jersey, 07921. Upon information and belief, Defendant Wockhardt USA is a wholly owned subsidiary of Wockhardt EU Operations (Swiss) AG, which in turn is a wholly owned subsidiary of Defendant

Wockhardt Ltd. Upon information and belief, Wockhardt USA is registered to do business in New Jersey and does business in this judicial district.

1.G. Defendant Wockhardt Ltd. and Defendant Wockhardt USA are collectively referred to as “Wockhardt.”

1.H. Upon information and belief, Defendant Reddy Ltd. is an Indian corporation having a place of business at 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh, India. Upon information and belief, Defendant Reddy Ltd., itself and through its wholly owned subsidiary and agent Defendant Reddy Inc., manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Defendants Reddy Ltd. and Reddy Inc. have appointed Bruce D. Radin, Esq. of Budd Lerner, P.C., which is located at 150 John F. Kennedy Parkway, 3rd Floor, Short Hills, New Jersey 07078, as their agent in New Jersey authorized to accept service of process in this action.

1.I. Upon information and belief, Defendant Reddy Inc. is a New Jersey corporation having a place of business at 200 Somerset Corporate Building, Bridgewater, New Jersey 08807 and is a wholly owned subsidiary and agent of Defendant Reddy Ltd. Upon information and belief, Reddy Inc. is registered to do business in New Jersey and does business in this judicial district.

1.J. Defendant Reddy Ltd. and Defendant Reddy Inc. are collectively referred to as “Reddy.”

1.K. Upon information and belief, Defendant Roxane is a Nevada corporation having a place of business at 1809 Wilson Road, Columbus, OH 43228. Upon information and belief, Defendant Roxane is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Roxane manufactures, markets and sells many

pharmaceutical products, including generic prescription drug products that are marketed and sold to customers in New Jersey. Upon information and belief, Roxane has previously consented to personal jurisdiction in this Court.

1.L. Upon information and belief, Defendant Cobalt Labs is a Delaware corporation and agent of Defendant Cobalt Pharma having a place of business at 24840 South Tamiami Trail, Bonita Springs, FL 34134. Upon information and belief, Defendant Cobalt Labs is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Cobalt Labs has previously admitted personal jurisdiction in this Court.

1.M. Upon information and belief, Defendant Cobalt Pharma is a Canadian corporation having a place of business at 6500 Kitimat Road, Mississauga, Ontario, Canada L5N 2B8. Upon information and belief, Defendant Cobalt Pharma, either directly or in concert with its agent Defendant Cobalt Labs, is engaged in the business of developing, manufacturing and/or selling pharmaceutical products, many of which are sold in New Jersey. Upon information and belief, Cobalt Pharma has previously admitted personal jurisdiction in this Court.

1.N. Defendant Cobalt Labs and Defendant Cobalt Pharma are collectively referred to as “Cobalt.”

1.O. Upon information and belief, Defendant Glenmark USA is a Delaware corporation having a place of business at 750 Corporate Drive, Mahwah, New Jersey 07430. Upon information and belief, Defendant Glenmark USA is a wholly owned subsidiary, division and agent of Glenmark Ltd. Upon information and belief, Defendant Glenmark USA, either directly or through its agents, is engaged in the business of importing, selling and distributing pharmaceutical products, many of which are sold in New Jersey. Defendant Glenmark USA is registered to do business in New Jersey and does business in this judicial district. Upon

information and belief, Defendant Glenmark USA has appointed Dr. Vijay Soni, Executive Vice President – IP, Glenmark Generics, Inc., 750 Corporate Drive, Mahwah, New Jersey 07430 as its agent in New Jersey authorized to accept service of process in this action.

1.P. Upon information and belief, Defendant Glenmark Ltd. is an Indian corporation having a place of business at Glenmark House, HDO - Corporate Bldg., Wing A, B. D. Sawant Marg, Chakala, Off Western Express Highway, Andheri [East], Mumbai, 400 099, India, and is a wholly owned subsidiary of Glenmark Pharma. Upon information and belief, Defendant Glenmark Ltd., either directly or through its agents, is engaged in the business of developing, manufacturing and selling pharmaceutical products, many of which are sold in New Jersey.

1.Q. Upon information and belief, Defendant Glenmark Pharma is an Indian corporation having a place of business at Glenmark House, HDO - Corporate Bldg., Wing A, B. D. Sawant Marg, Chakala, Off Western Express Highway, Andheri [East], Mumbai, 400 099, India. Upon information and belief, Defendant Glenmark Pharma, either directly or through its agents, is engaged in the business of developing, manufacturing and selling pharmaceutical products, many of which are sold in New Jersey.

1.R. Defendant Glenmark USA, Defendant Glenmark Ltd. and Defendant Glenmark Pharma are collectively referred to as “Glenmark.”

1.S. Upon information and belief, Defendant Orchid Healthcare is an unincorporated division of Defendant Orchid Ltd., having a place of business at Plot No. B3-B6 & B11-B14, Sipcot Industrial Park, Irungattukottai, Sriperumbudur (TK) - 602 105, Kancheepuram District, Tamil Nadu, India. Upon information and belief, Defendant Orchid Healthcare, itself and through Defendants Orchid Ltd. and Orgenus, markets and sells generic

drugs throughout the United States, including in this judicial district. Upon information and belief, Defendant Orchid Healthcare has previously admitted personal jurisdiction in this Court.

1.T. Upon information and belief, Defendant Orchid Ltd. is an Indian corporation having a place of business at Orchid Towers, #313, Valluvar Kottam High Road, Nungambakkam, Chennai - 600 034, Tamil Nadu, India. Upon information and belief, Defendant Orchid Ltd., itself and through its wholly owned subsidiary and agent Defendant Orgenus, manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Defendant Orchid Ltd. is registered to do business in New Jersey and does business in this judicial district. Defendant Orchid Ltd. has previously admitted personal jurisdiction in this Court.

1.U. Upon information and belief, Defendant Orgenus is a New Jersey corporation having a place of business at 700 Alexander Park, Suite 104, Princeton, New Jersey 08540. Upon information and belief, Defendant Orgenus is a wholly owned subsidiary and agent of Defendant Orchid Ltd. Upon information and belief, Orgenus is registered to do business in New Jersey and does business in this judicial district. Defendant Orgenus has previously admitted personal jurisdiction in this Court.

1.V. Defendant Orchid Healthcare, Defendant Orchid Ltd., and Defendant Orgenus are collectively referred to as “Orchid.”

1.W. Upon information and belief, Defendant Lupin Pharma is a Virginia corporation having a place of business at Harborplace Tower, 111 South Calvert Street, 21st Floor, Baltimore, Maryland 21202 and is a wholly owned subsidiary and agent of Defendant Lupin Ltd. Upon information and belief, Defendant Lupin Pharma sells various drug products in the United States, including in this judicial district. Upon information and belief, Defendant

Lupin Pharma is registered to do business in New Jersey and does business in this judicial district.

1.X. Upon information and belief, Defendant Lupin Ltd. is an Indian corporation having a place of business at Laxmi Towers, B Wing, Bandra Kurla Complex, Bandra (East), Mumbai, Maharashtra 400 051, India. Upon information and belief, Defendant Lupin Ltd., itself and through its wholly owned subsidiary and agent Lupin Pharma, manufactures, sells and/or markets generic drugs for sale and use throughout the United States, including in this judicial district.

1.Y. Defendant Lupin Pharma and Defendant Lupin Ltd. are collectively referred to as “Lupin.”

1.Z. Upon information and belief, Defendant Sun Global is a corporation organized under the laws of the British Virgin Islands maintaining a post office box at International Trust Building, P.O. Box No. 659, Road Town, Tortola, British Virgin Islands. Upon information and belief, Defendant Sun Global is a wholly owned subsidiary of Defendant Sun Pharma Ltd. Upon information and belief, Sun Global has appointed John Dauer Jr. Esq., Chief Patent Counsel, Sun Pharmaceutical Industries, Inc., 270 Prospect Plains Road, Cranbury, New Jersey 08512 as its agent in New Jersey authorized to accept service of process in this action and to accept written notice requesting access to Sun Global’s confidential information under Sun Global’s Offer of Confidential Access. Upon information and belief, Defendant Sun Global acts in concert with Sun Pharma Inc. and/or Sun Pharma Ltd. to support the sales and marketing of pharmaceutical products for sale and use throughout the United States, including in this judicial district.

1.AA. Upon information and belief, Defendant Sun Pharma Inc. is a Michigan corporation and conducts business in the State of New Jersey at its offices located at 270 Prospect Plains Road, Cranbury, New Jersey 08512. Upon information and belief, Defendant Sun Pharma Inc. is a wholly owned subsidiary and agent of Defendant Sun Pharma Ltd. Upon information and belief, Dr. Ratnesh Shrivastava, Dr. Bharati Nadkarni and John Dauer Jr., Esq., all of Sun Pharma Inc., 270 Prospect Plains Road, Cranbury, New Jersey 08512 are authorized to negotiate and did negotiate access to Sun Global's confidential information under Sun Global's Offer of Confidential Access. Upon information and belief, Defendant Sun Pharma Inc. is an agent of Defendant Sun Global. Upon information and belief, Sun Pharma Inc. is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Sun Pharma Inc. has previously admitted personal jurisdiction in this Court.

1.BB. Upon information and belief, Defendant Sun Pharma Ltd. is a public limited liability company incorporated and existing under the laws of India having a place of business at Acme Plaza, Andheri-Kurla Road, Andheri [East], Mumbai 400 059 Maharashtra, India. Upon information and belief, Defendant Sun Pharma Ltd., itself and through its wholly owned subsidiary and agent Defendant Sun Pharma Inc., manufactures, sells and/or markets generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Sun Pharma Ltd. has previously admitted personal jurisdiction in this Court.

1.CC. Defendant Sun Global, Defendant Sun Pharma Inc. and Defendant Sun Pharma Ltd. are collectively referred to as "Sun."

1.DD. Upon information and belief, Defendant Alphapharm Ltd. is an Australian corporation having a place of business at Chase Building 2, 1 Wentworth Park Road, Glebe

NSW 2037, Australia. Upon information and belief, Defendant Alphapharm Ltd. derives substantial revenue from interstate and/or international commerce. Upon information and belief, Defendant Alphapharm Ltd. has received FDA approval to sell drug products throughout the United States, including into this judicial district. Upon information and belief, Defendant Alphapharm Ltd. conducts business in this judicial district. Upon information and belief, Defendant Alphapharm Ltd. is a wholly owned subsidiary of Mylan Australia Pty., Ltd., which is a wholly owned subsidiary of Defendant Mylan Inc. Upon information and belief, Defendant Alphapharm Ltd. has previously consented to personal jurisdiction in this Court.

1.EE. Upon information and belief, Defendant Mylan Inc. is a corporation organized under the laws of Pennsylvania having a place of business at One Woodbridge Center, 9th Floor, Suite 920, Woodbridge, New Jersey, 07095. Upon information and belief, Defendant Mylan Inc., itself and through Defendant Alphapharm Ltd., manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Defendant Mylan Inc. is registered to do business in New Jersey, has solicited employees to work in this judicial district, and does business in this judicial district.

1.FF. Defendant Alphapharm Ltd. and Defendant Mylan Inc. are collectively referred to as “Alphapharm.”

NATURE OF THE ACTION

2. This is a civil action for the infringement of United States Patent No. 6,864,257 (“the ’257 patent”), United States Patent No. 6,319,926 (“the ’926 patent”), United States Patent No. 6,444,673 (“the ’673 patent”) and United States Patent No. 7,381,724 (“the ’724 patent”). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.*

JURISDICTION AND VENUE

3. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this Court as to each Defendant pursuant to 28 U.S.C. §§ 1391(b), (c) and/or (d) and 1400(b).

4. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiff Sepracor. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth above and below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

5. This Court has personal jurisdiction over Defendant Teva USA.

6. This Court has personal jurisdiction over Defendant Teva Ltd.

7. This Court has personal jurisdiction over Defendant Wockhardt USA, and for this case, Wockhardt USA has consented in an email dated March 17, 2009 to personal jurisdiction and venue in this judicial district.

8. This Court has personal jurisdiction over Defendant Wockhardt Ltd., and for this case, Wockhardt Ltd. has consented in an email dated March 17, 2009 to personal jurisdiction and venue in this judicial district.

9. This Court has personal jurisdiction over Defendant Reddy Inc., and for this case, Reddy Inc. has consented in an email dated March 11, 2009 to personal jurisdiction and venue in this judicial district.

10. This Court has personal jurisdiction over Defendant Reddy Ltd., and for this case, Reddy Ltd. has consented in an email dated March 11, 2009 to personal jurisdiction and venue in this judicial district.

11. This Court has personal jurisdiction over Defendant Roxane.

12. This Court has personal jurisdiction over Defendant Cobalt Labs.

13. This Court has personal jurisdiction over Defendant Cobalt Pharma.

14. This Court has personal jurisdiction over Defendant Glenmark USA, and for this case, Glenmark USA has consented in a letter dated March 13, 2009 to personal jurisdiction and venue in this judicial district.

15. This Court has personal jurisdiction over Defendant Glenmark Ltd., and for this case, Glenmark Ltd. has consented in a letter dated March 13, 2009 to personal jurisdiction and venue in this judicial district.

16. This Court has personal jurisdiction over Defendant Glenmark Pharma.

17. This Court has personal jurisdiction over Defendant Orchid Healthcare.

18. This Court has personal jurisdiction over Defendant Orchid Ltd.

19. This Court has personal jurisdiction over Defendant Orgenus.

20. This Court has personal jurisdiction over Defendant Lupin Pharma, and for this case, Lupin Pharma has consented in an email dated March 16, 2009 to personal jurisdiction and venue in this judicial district.

21. This Court has personal jurisdiction over Defendant Lupin Ltd., and for this case, Lupin Ltd. has consented in an email dated March 16, 2009 to personal jurisdiction and venue in this judicial district.

22. This Court has personal jurisdiction over Defendant Sun Global.

23. This Court has personal jurisdiction over Defendant Sun Pharma Inc.

24. This Court has personal jurisdiction over Defendant Sun Pharma Ltd.

25. This Court has personal jurisdiction over Defendant Alphapharm Ltd.

26. This Court has personal jurisdiction over Defendant Mylan Inc.

THE PATENTS

27. On March 8, 2005, the '257 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing It," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '257 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '257 patent is attached hereto as Exhibit A.

28. On September 3, 2002, the '673 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing It," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '673 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '673 patent is attached hereto as Exhibit B.

29. On November 20, 2001, the '926 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing It," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '926 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '926 patent is attached hereto as Exhibit C.

30. On June 3, 2008, the '724 patent, titled "Optically Active 5H-Pyrrolo[3,4-B] Pyrazine Derivative, Its Preparation and Pharmaceutical Compositions Containing Same," was duly and legally issued to Sepracor as assignee. Since that time, Sepracor has been, and continues to be, the sole owner of the '724 patent and the sole owner of the right to sue and to

recover for any infringement of that patent. A copy of the '724 patent is attached hereto as Exhibit D.

ACTS GIVING RISE TO THIS ACTION

INFRINGEMENT OF THE '257 PATENT

COUNT I – INFRINGEMENT OF THE '257 PATENT BY TEVA

31. Plaintiff realleges paragraphs 1-30 as if fully set forth herein.

32. Upon information and belief, Defendant Teva submitted ANDA No. 91-169 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-169 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-169 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

33. ANDA No. 91-169 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are invalid. Sepracor received written notification of ANDA No. 91-169 and the § 505(j)(2)(A)(vii)(IV) allegations on February 9, 2009.

34. Teva's submission to the FDA of ANDA No. 91-169, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

35. Teva USA and Teva Ltd. are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Teva USA and Teva Ltd. actively and knowingly caused to be submitted, assisted with, participated in,

contributed to and/or directed the submission of ANDA No. 91-169 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

36. Teva's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-169 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Teva's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

37. Upon information and belief, Teva was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

38. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

39. Sepracor will be irreparably harmed by Teva's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT II – INFRINGEMENT OF THE '257 PATENT BY REDDY

40. Plaintiff realleges paragraphs 1-39 as if fully set forth herein.

41. Upon information and belief, Defendant Reddy submitted ANDA No. 91-024 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-024 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-024 specifically seeks

FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

42. ANDA No. 91-024 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations on February 17, 2009.

43. Reddy's submission to the FDA of ANDA No. 91-024, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

44. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

45. Reddy's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Reddy's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

46. Upon information and belief, Reddy was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

47. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

48. Sepracor will be irreparably harmed by Reddy's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT III – INFRINGEMENT OF THE '257 PATENT BY ROXANE

49. Plaintiff realleges paragraphs 1-48 as if fully set forth herein.

50. Upon information and belief, Defendant Roxane submitted ANDA No. 91-153 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-153 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-153 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

51. ANDA No. 91-153 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-153 and the § 505(j)(2)(A)(vii)(IV) allegations on February 23, 2009.

52. Roxane's submission to the FDA of ANDA No. 91-153, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

53. Roxane's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

54. Upon information and belief, Roxane was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

55. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

56. Sepracor will be irreparably harmed by Roxane's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT IV – INFRINGEMENT OF THE '257 PATENT BY COBALT

57. Plaintiff realleges paragraphs 1-56 as if fully set forth herein.

58. Upon information and belief, Defendant Cobalt submitted ANDA No. 91-150 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-150 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-150 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

59. ANDA No. 91-150 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or unenforceable. Sepracor received written notification of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations on February 12, 2009.

60. Cobalt's submission to the FDA of ANDA No. 91-150, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

61. Cobalt Labs and Cobalt Pharma are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Cobalt Labs and Cobalt Pharma actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

62. Cobalt's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Cobalt's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

63. Upon information and belief, Cobalt was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

64. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

65. Sepracor will be irreparably harmed by Cobalt's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT V – INFRINGEMENT OF THE '257 PATENT BY GLENMARK

66. Plaintiff realleges paragraphs 1-65 as if fully set forth herein.

67. Upon information and belief, Defendant Glenmark submitted ANDA No. 91-166 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-166 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-166 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

68. ANDA No. 91-166 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

69. Glenmark's submission to the FDA of ANDA No. 91-166, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

70. Glenmark USA, Glenmark Ltd. and Glenmark Pharma are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and

belief, Glenmark USA, Glenmark Ltd. and Glenmark Pharma actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

71. Glenmark's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Glenmark's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

72. Upon information and belief, Glenmark was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

73. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

74. Sepracor will be irreparably harmed by Glenmark's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT VI – INFRINGEMENT OF THE '257 PATENT BY ORCHID

75. Plaintiff realleges paragraphs 1-74 as if fully set forth herein.

76. Upon information and belief, Defendant Orchid submitted ANDA No. 91-113 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-113 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient

eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-113 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

77. ANDA No. 91-113 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

78. Orchid's submission to the FDA of ANDA No. 91-113, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

79. Orchid Healthcare, Orchid Ltd. and Orgenus are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Orchid Healthcare, Orchid Ltd. and Orgenus actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

80. Orchid's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Orchid's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

81. Upon information and belief, Orchid was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

82. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

83. Sepracor will be irreparably harmed by Orchid's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT VII – INFRINGEMENT OF THE '257 PATENT BY LUPIN

84. Plaintiff realleges paragraphs 1-83 as if fully set forth herein.

85. Upon information and belief, Defendant Lupin submitted ANDA No. 91-124 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-124 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-124 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

86. ANDA No. 91-124 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations on February 24, 2009.

87. Lupin's submission to the FDA of ANDA No. 91-124, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

88. Lupin Pharma and Lupin Ltd. are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Lupin Pharma and Lupin Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

89. Lupin's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Lupin's commercial manufacture, use, offer for sale, importation or sale its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

90. Upon information and belief, Lupin was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

91. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

92. Sepracor will be irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT VIII – INFRINGEMENT OF THE '257 PATENT BY SUN

93. Plaintiff realleges paragraphs 1-92 as if fully set forth herein.

94. Upon information and belief, Defendant Sun submitted ANDA No. 91-103 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-103 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-103 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

95. ANDA No. 91-103 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations on February 25, 2009.

96. Sun's submission to the FDA of ANDA No. 91-103, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

97. Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

98. Sun's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C.

§ 271(e)(2)(A). Sun's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

99. Upon information and belief, Sun was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

100. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

101. Sepracor will be irreparably harmed by Sun's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT IX – INFRINGEMENT OF THE '257 PATENT BY ALPHAPHARM

102. Plaintiff realleges paragraphs 1-101 as if fully set forth herein.

103. Upon information and belief, Defendant Alphapharm submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '257 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '257 patent.

104. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '257 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

105. Alphapharm's submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A).

106. Alphapharm Ltd. and Mylan Inc. are jointly and severally liable for any infringement of the '257 patent. This is because, upon information and belief, Alphapharm Ltd. and Mylan Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

107. Alphapharm's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '257 patent under 35 U.S.C. § 271(e)(2)(A). Alphapharm's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '257 patent under 35 U.S.C. § 271(a), (b) and/or (c).

108. Upon information and belief, Alphapharm was aware of the existence of the '257 patent and was aware that filing of the ANDA and certification with respect to the '257 patent constituted an act of infringement of that patent.

109. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

110. Sepracor will be irreparably harmed by Alphapharm's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

INFRINGEMENT OF THE '673 PATENT

COUNT X – INFRINGEMENT OF THE '673 PATENT BY WOCKHARDT

111. Plaintiff realleges paragraphs 1-110 as if fully set forth herein.

112. Upon information and belief, Defendant Wockhardt submitted ANDA No. 91-165 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-165 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-165 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

113. ANDA No. 91-165 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are invalid. Sepracor received written notification of ANDA No. 91-165 and the § 505(j)(2)(A)(vii)(IV) allegations on February 26, 2009.

114. Wockhardt's submission to the FDA of ANDA No. 91-165, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

115. Wockhardt Ltd. and Wockhardt USA are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Wockhardt Ltd. and Wockhardt USA actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-165 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

116. Wockhardt's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-165 and the

§ 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C.

§ 271(e)(2)(A). Wockhardt's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

117. Upon information and belief, Wockhardt was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

118. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

119. Sepracor will be irreparably harmed by Wockhardt's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XI – INFRINGEMENT OF THE '673 PATENT BY REDDY

120. Plaintiff realleges paragraphs 1-119 as if fully set forth herein.

121. Upon information and belief, Defendant Reddy submitted ANDA No. 91-024 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-024 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-024 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

122. ANDA No. 91-024 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are either invalid or not infringed

by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations on February 17, 2009.

123. Reddy's submission to the FDA of ANDA No. 91-024, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

124. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

125. Reddy's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Reddy's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

126. Upon information and belief, Reddy was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

127. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

128. Sepracor will be irreparably harmed by Reddy's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XII – INFRINGEMENT OF THE '673 PATENT BY ROXANE

129. Plaintiff realleges paragraphs 1-128 as if fully set forth herein.

130. Upon information and belief, Defendant Roxane submitted ANDA No. 91-153 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-153 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-153 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

131. ANDA No. 91-153 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-153 and the § 505(j)(2)(A)(vii)(IV) allegation on February 23, 2009.

132. Roxane's submission to the FDA of ANDA No. 91-153, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

133. Roxane's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

134. Upon information and belief, Roxane was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

135. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

136. Sepracor will be irreparably harmed by Roxane's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XIII – INFRINGEMENT OF THE '673 PATENT BY COBALT

137. Plaintiff realleges paragraphs 1-136 as if fully set forth herein.

138. Upon information and belief, Defendant Cobalt submitted ANDA No. 91-150 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-150 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-150 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

139. ANDA No. 91-150 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are either invalid or unenforceable. Sepracor received written notification of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations on February 12, 2009.

140. Cobalt's submission to the FDA of ANDA No. 91-150, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

141. Cobalt Labs and Cobalt Pharma are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Cobalt Labs and Cobalt Pharma actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

142. Cobalt's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Cobalt's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

143. Upon information and belief, Cobalt was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

144. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

145. Sepracor will be irreparably harmed by Cobalt's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XIV – INFRINGEMENT OF THE '673 PATENT BY GLENMARK

146. Plaintiff realleges paragraphs 1-145 as if fully set forth herein.

147. Upon information and belief, Defendant Glenmark submitted ANDA No. 91-166 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.

§ 355(j)). ANDA No. 91-166 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-166 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

148. ANDA No. 91-166 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

149. Glenmark's submission to the FDA of ANDA No. 91-166, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

150. Glenmark USA, Glenmark Ltd. and Glenmark Pharma are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief Glenmark USA, Glenmark Ltd. and Glenmark Pharma actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

151. Glenmark's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Glenmark's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or

contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

152. Upon information and belief, Glenmark was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

153. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

154. Sepracor will be irreparably harmed by Glenmark's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XV – INFRINGEMENT OF THE '673 PATENT BY ORCHID

155. Plaintiff realleges paragraphs 1-154 as if fully set forth herein.

156. Upon information and belief, Defendant Orchid submitted ANDA No. 91-113 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-113 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-113 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

157. ANDA No. 91-113 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

158. Orchid's submission to the FDA of ANDA No. 91-113, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

159. Orchid Healthcare, Orchid Ltd. and Orgenus are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Orchid Healthcare, Orchid Ltd. and Orgenus actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

160. Orchid's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Orchid's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

161. Upon information and belief, Orchid was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

162. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

163. Sepracor will be irreparably harmed by Orchid's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XVI – INFRINGEMENT OF THE '673 PATENT BY LUPIN

164. Plaintiff realleges paragraphs 1-163 as if fully set forth herein.

165. Upon information and belief, Defendant Lupin submitted ANDA No. 91-124 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-124 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-124 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

166. ANDA No. 91-124 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are invalid. Sepracor received written notification of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations on February 24, 2009.

167. Lupin's submission to the FDA of ANDA No. 91-124, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

168. Lupin Pharma and Lupin Ltd. are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Lupin Pharma and Lupin Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

169. Lupin's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C.

§ 271(e)(2)(A). Lupin's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

170. Upon information and belief, Lupin was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

171. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

172. Sepracor will be irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XVII – INFRINGEMENT OF THE '673 PATENT BY SUN

173. Plaintiff realleges paragraphs 1-172 as if fully set forth herein.

174. Upon information and belief, Defendant Sun submitted ANDA No. 91-103 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-103 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-103 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

175. ANDA No. 91-103 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Sepracor's Lunesta[®] brand

products. Sepracor received written notification of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations on February 25, 2009.

176. Sun's submission to the FDA of ANDA No. 91-103, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

177. Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

178. Sun's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Sun's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

179. Upon information and belief, Sun was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

180. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

181. Sepracor will be irreparably harmed by Sun's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XVIII – INFRINGEMENT OF THE '673 PATENT BY ALPHAPHARM

182. Plaintiff realleges paragraphs 1-181 as if fully set forth herein.

183. Upon information and belief, Defendant Alphapharm submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '673 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '673 patent.

184. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '673 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

185. Alphapharm's submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A).

186. Alphapharm Ltd. and Mylan Inc. are jointly and severally liable for any infringement of the '673 patent. This is because, upon information and belief, Alphapharm Ltd. and Mylan Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

187. Alphapharm's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '673 patent under 35 U.S.C. § 271(e)(2)(A). Alphapharm's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '673 patent under 35 U.S.C. § 271(a), (b) and/or (c).

188. Upon information and belief, Alphapharm was aware of the existence of the '673 patent and was aware that filing of the ANDA and certification with respect to the '673 patent constituted an act of infringement of that patent.

189. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

190. Sepracor will be irreparably harmed by Alphapharm's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

INFRINGEMENT OF THE '926 PATENT

COUNT XIX– INFRINGEMENT OF THE '926 PATENT BY REDDY

191. Plaintiff realleges paragraphs 1-190 as if fully set forth herein.

192. Upon information and belief, Defendant Reddy submitted ANDA No. 91-024 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-024 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-024 specifically seeks

FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

193. ANDA No. 91-024 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations on February 17, 2009.

194. Reddy's submission to the FDA of ANDA No. 91-024, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

195. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

196. Reddy's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Reddy's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

197. Upon information and belief, Reddy was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

198. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

199. Sepracor will be irreparably harmed by Reddy's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XX – INFRINGEMENT OF THE '926 PATENT BY ROXANE

200. Plaintiff realleges paragraphs 1-199 as if fully set forth herein.

201. Upon information and belief, Defendant Roxane submitted ANDA No. 91-153 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-153 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-153 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

202. ANDA No. 91-153 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-153 and the § 505(j)(2)(A)(vii)(IV) allegations on February 23, 2009.

203. Roxane's submission to the FDA of ANDA No. 91-153, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

204. Roxane's commercial use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

205. Upon information and belief, Roxane was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

206. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

207. Sepracor will be irreparably harmed by Roxane's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXI – INFRINGEMENT OF THE '926 PATENT BY COBALT

208. Plaintiff realleges paragraphs 1-207 as if fully set forth herein.

209. Upon information and belief, Defendant Cobalt, submitted ANDA No. 91-150 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-150 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-150 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

210. ANDA No. 91-150 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are either invalid or unenforceable. Sepracor received written notification of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations on February 12, 2009.

211. Cobalt's submission to the FDA of ANDA No. 91-150, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

212. Cobalt Labs and Cobalt Pharma are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Cobalt Labs and Cobalt Pharma actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

213. Cobalt's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Cobalt's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

214. Upon information and belief, Cobalt was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

215. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

216. Sepracor will be irreparably harmed by Cobalt's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXII – INFRINGEMENT OF THE '926 PATENT BY GLENMARK

217. Plaintiff realleges paragraphs 1-216 as if fully set forth herein.

218. Upon information and belief, Defendant Glenmark submitted ANDA No. 91-166 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-166 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-166 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

219. ANDA No. 91-166 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are invalid. Sepracor received written notification of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

220. Glenmark's submission to the FDA of ANDA No. 91-166, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

221. Glenmark USA, Glenmark Ltd. and Glenmark Pharma are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Glenmark USA, Glenmark Ltd. and Glenmark Pharma actively and knowingly caused to

be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

222. Glenmark's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Glenmark's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand product, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

223. Upon information and belief, Glenmark was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

224. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

225. Sepracor will be irreparably harmed by Glenmark's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXIII – INFRINGEMENT OF THE '926 PATENT BY ORCHID

226. Plaintiff realleges paragraphs 1-225 as if fully set forth herein.

227. Upon information and belief, Defendant Orchid submitted ANDA No. 91-113 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-113 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-113 specifically seeks

FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

228. ANDA No. 91-113 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

229. Orchid's submission to the FDA of ANDA No. 91-113, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

230. Orchid Healthcare, Orchid Ltd. and Orgenus are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Orchid Healthcare, Orchid Ltd. and Orgenus actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

231. Orchid's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Orchid's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

232. Upon information and belief, Orchid was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

233. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

234. Sepracor will be irreparably harmed by Orchid's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXIV – INFRINGEMENT OF THE '926 PATENT BY LUPIN

235. Plaintiff realleges paragraphs 1-234 as if fully set forth herein.

236. Upon information and belief, Defendant Lupin submitted ANDA No. 91-124 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-124 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-124 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

237. ANDA No. 91-124 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are invalid. Sepracor received written notification of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations on February 24, 2009.

238. Lupin's submission to the FDA of ANDA No. 91-124, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

239. Lupin Pharma and Lupin Ltd. are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Lupin Pharma and Lupin Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

240. Lupin's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Lupin's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

241. Upon information and belief, Lupin was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

242. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

243. Sepracor will be irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXV – INFRINGEMENT OF THE '926 PATENT BY SUN

244. Plaintiff realleges paragraphs 1-243 as if fully set forth herein.

245. Upon information and belief, Defendant Sun submitted ANDA No. 91-103 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-103 seeks the FDA approval necessary to engage in the commercial manufacture,

use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-103 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

246. ANDA No. 91-103 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are invalid. Sepracor received written notification of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations on February 25, 2009.

247. Sun's submission to the FDA of ANDA No. 91-103, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

248. Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

249. Sun's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Sun's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

250. Upon information and belief, Sun was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

251. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

252. Sepracor will be irreparably harmed by Sun's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXVI – INFRINGEMENT OF THE '926 PATENT BY ALPHAPHARM

253. Plaintiff realleges paragraphs 1-252 as if fully set forth herein.

254. Upon information and belief, Defendant Alphapharm submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '926 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '926 patent.

255. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '926 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

256. Alphapharm's submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A).

257. Alphapharm Ltd. and Mylan Inc. are jointly and severally liable for any infringement of the '926 patent. This is because, upon information and belief, Alphapharm Ltd. and Mylan Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

258. Alphapharm's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '926 patent under 35 U.S.C. § 271(e)(2)(A). Alphapharm's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '926 patent under 35 U.S.C. § 271(a), (b) and/or (c).

259. Upon information and belief, Alphapharm was aware of the existence of the '926 patent and was aware that filing of the ANDA and certification with respect to the '926 patent constituted an act of infringement of that patent.

260. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

261. Sepracor will be irreparably harmed by Alphapharm's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

INFRINGEMENT OF THE '724 PATENT

COUNT XXVII – INFRINGEMENT OF THE '724 PATENT BY REDDY

262. Plaintiff realleges paragraphs 1-261 as if fully set forth herein.

263. Upon information and belief, Defendant Reddy submitted ANDA No. 91-024 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-024 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-024 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

264. ANDA No. 91-024 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid. Sepracor received written notification of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations on February 17, 2009.

265. Reddy's submission to the FDA of ANDA No. 91-024, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

266. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

267. Reddy's active and knowing participation in, contribution to aiding, abetting and/or inducement of the submission of ANDA No. 91-024 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Reddy's commercial use, offer for sale, importation or sale of its

proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

268. Upon information and belief, Reddy was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

269. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

270. Sepracor will be irreparably harmed by Reddy's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXVIII – INFRINGEMENT OF THE '724 PATENT BY ROXANE

271. Plaintiff realleges paragraphs 1-270 as if fully set forth herein.

272. Upon information and belief, Defendant Roxane submitted ANDA No. 91-153 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-153 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-153 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

273. ANDA No. 91-153 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are either invalid, unenforceable or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's

Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-153 and the § 505(j)(2)(A)(vii)(IV) allegations on February 23, 2009.

274. Roxane's submission to the FDA of ANDA No. 91-153, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Roxane's commercial use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

275. Upon information and belief, Defendant Roxane was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

276. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

277. Sepracor will be irreparably harmed by Defendant Roxane's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXIX – INFRINGEMENT OF THE '724 PATENT BY COBALT

278. Plaintiff realleges paragraphs 1-277 as if fully set forth herein.

279. Upon information and belief, Defendant Cobalt submitted ANDA No. 91-150 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-150 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-150 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

280. ANDA No. 91-150 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are either invalid or unenforceable. Sepracor received written notification of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations on February 12, 2009.

281. Cobalt's submission to the FDA of ANDA No. 91-150, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

282. Cobalt Labs and Cobalt Pharma are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Cobalt Labs and Cobalt Pharma actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission to the FDA of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations.

283. Cobalt's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-150 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Cobalt's commercial use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

284. Upon information and belief, Cobalt was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

285. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

286. Sepracor will be irreparably harmed by Cobalt's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXX – INFRINGEMENT OF THE '724 PATENT BY GLENMARK

287. Plaintiff realleges paragraphs 1-286 as if fully set forth herein.

288. Upon information and belief, Defendant Glenmark submitted ANDA No. 91-166 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-166 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale, importation and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-166 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

289. ANDA No. 91-166 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid. Sepracor received written notification of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

290. Glenmark's submission to the FDA of ANDA No. 91-166, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

291. Glenmark USA, Glenmark Ltd. and Glenmark Pharma are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief Glenmark USA, Glenmark Ltd. and Glenmark Pharma actively and knowingly caused to

be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

292. Glenmark's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-166 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Glenmark's commercial use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

293. Upon information and belief, Glenmark was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

294. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

295. Sepracor will be irreparably harmed by Glenmark's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXXI – INFRINGEMENT OF THE '724 PATENT BY ORCHID

296. Plaintiff realleges paragraphs 1-295 as if fully set forth herein.

297. Upon information and belief, Defendant Orchid submitted ANDA No. 91-113 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-113 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-113 specifically seeks

FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

298. ANDA No. 91-113 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations on February 20, 2009.

299. Orchid's submission to the FDA of ANDA No. 91-113, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

300. Orchid Healthcare, Orchid Ltd. and Orgenus are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Orchid Healthcare, Orchid Ltd. and Orgenus actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

301. Orchid's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 91-113 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Orchid's commercial use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

302. Upon information and belief, Orchid was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

303. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

304. Sepracor will be irreparably harmed by Orchid's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXXII – INFRINGEMENT OF THE '724 PATENT BY LUPIN

305. Plaintiff realleges paragraphs 1-304 as if fully set forth herein.

306. Upon information and belief, Defendant Lupin submitted ANDA No. 91-124 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 91-124 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-124 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

307. ANDA No. 91-124 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Sepracor's Lunesta[®] brand products. Sepracor received written notification of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations on February 24, 2009.

308. Lupin's submission to the FDA of ANDA No. 91-124, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

309. Lupin Pharma and Lupin Ltd. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Lupin Pharma and Lupin Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

310. Lupin's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 91-124 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Lupin's commercial use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

311. Upon information and belief, Lupin was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

312. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

313. Sepracor will be irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXXIII – INFRINGEMENT OF THE '724 PATENT BY SUN

314. Plaintiff realleges paragraphs 1-313 as if fully set forth herein.

315. Upon information and belief, Defendant Sun submitted ANDA No. 91-103 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-103 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-103 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta® brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

316. ANDA No. 91-103 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Sepracor's Lunesta® brand products. Sepracor received written notification of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations on February 25, 2009.

317. Sun's submission to the FDA of ANDA No. 91-103, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

318. Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Sun Global, Sun Pharma Inc. and Sun Pharma Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

319. Sun's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-103 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C.

§ 271(e)(2)(A). Sun's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

320. Upon information and belief, Sun was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

321. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

322. Sepracor will be irreparably harmed by Sun's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

COUNT XXXIV – INFRINGEMENT OF THE '724 PATENT BY ALPHAPHARM

323. Plaintiff realleges paragraphs 1-322 as if fully set forth herein.

324. Upon information and belief, Defendant Alphapharm submitted ANDA No. 91-151 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(i)). ANDA No. 91-151 seeks the FDA approval necessary to engage in the commercial manufacture, use and sale of generic tablets containing 1 mg, 2 mg or 3 mg of the active ingredient eszopiclone prior to the expiration of the '724 patent. ANDA No. 91-151 specifically seeks FDA approval to market a proposed generic version of Sepracor's Lunesta[®] brand 1 mg, 2 mg and 3 mg eszopiclone tablets prior to the expiration of the '724 patent.

325. ANDA No. 91-151 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid. Sepracor received written notification of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations on March 10, 2009.

326. Alphapharm's submission to the FDA of ANDA No. 91-151, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

327. Alphapharm Ltd. and Mylan Inc. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Alphapharm Ltd. and Mylan Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to and/or directed the submission of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

328. Alphapharm's active and knowing participation in, contribution to, aiding, abetting and/or inducement of the submission to the FDA of ANDA No. 91-151 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A). Alphapharm's commercial manufacture, use, offer for sale, importation or sale of its proposed generic versions of Sepracor's Lunesta[®] brand products, or inducement of or contribution to any such conduct, would further infringe the '724 patent under 35 U.S.C. § 271(a), (b) and/or (c).

329. Upon information and belief, Alphapharm was aware of the existence of the '724 patent and was aware that filing of the ANDA and certification with respect to the '724 patent constituted an act of infringement of that patent.

330. This case is an exceptional one and Sepracor is entitled to an award of its reasonable attorney fees under 35 U.S.C. § 285.

331. Sepracor will be irreparably harmed by Alphapharm's infringing activities unless those activities are enjoined by this Court. Sepracor does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Sepracor requests that:

A. A Judgment be entered declaring that Defendants Teva USA, Teva Ltd., Reddy Ltd., Reddy Inc., Roxane, Cobalt Labs, Cobalt Pharma, Glenmark USA, Glenmark Ltd., Glenmark Pharma, Orchid Healthcare, Orchid Ltd., Orgenus, Lupin Pharma, Lupin Ltd., Sun Global, Sun Pharma Inc., Sun Pharma Ltd., Alphapharm Ltd. and Mylan Inc. have infringed the '257 patent by submitting the aforesaid ANDAs;

B. A Judgment be entered declaring that Defendants Wockhardt USA, Wockhardt Ltd., Reddy Ltd., Reddy Inc., Roxane, Cobalt Labs, Cobalt Pharma, Glenmark USA, Glenmark Ltd., Glenmark Pharma, Orchid Healthcare, Orchid Ltd., Orgenus, Lupin Pharma, Lupin Ltd., Sun Global, Sun Pharma Inc., Sun Pharma Ltd., Alphapharm Ltd. and Mylan Inc. have infringed the '673 patent by submitting the aforesaid ANDAs;

C. A Judgment be entered declaring that Defendants Reddy Ltd., Reddy Inc., Roxane, Cobalt Labs, Cobalt Pharma, Glenmark USA, Glenmark Ltd., Glenmark Pharma, Orchid Healthcare, Orchid Ltd., Orgenus, Lupin Pharma, Lupin Ltd., Sun Global, Sun Pharma Inc., Sun Pharma Ltd., Alphapharm Ltd. and Mylan Inc. have infringed the '926 and '724 patents by submitting the aforesaid ANDAs;

D. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of any of Defendants' ANDAs identified in this Complaint be a date that is not earlier than the expiration dates of the '257 patent, '673 patent, '926 patent and '724 patent, or any later expiration of exclusivity for the '257 patent, '673 patent, '926 patent or '724 patent to which Plaintiff is or becomes entitled;

E. An Order be issued that Defendants Teva USA, Teva Ltd., Reddy Ltd., Reddy Inc., Roxane, Cobalt Labs, Cobalt Pharma, Glenmark USA, Glenmark Ltd., Glenmark Pharma, Orchid Healthcare, Orchid Ltd., Orgenus, Lupin Pharma, Lupin Ltd., Sun Global, Sun Pharma Inc., Sun Pharma Ltd., Alphapharm Ltd. and Mylan Inc., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing or selling the proposed generic versions of Sepracor's Lunesta[®] brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '257 patent, prior to the expiration of the '257 patent, including any extensions to which Plaintiff is or becomes entitled;

F. An Order be issued that Defendants Wockhardt USA, Wockhardt Ltd., Reddy Ltd., Reddy Inc., Roxane, Cobalt Labs, Cobalt Pharma, Glenmark USA, Glenmark Ltd., Glenmark Pharma, Orchid Healthcare, Orchid Ltd., Orgenus, Lupin Pharma, Lupin Ltd., Sun Global, Sun Pharma Inc., Sun Pharma Ltd., Alphapharm Ltd. and Mylan Inc., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing or selling the proposed generic versions of Sepracor's Lunesta[®] brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '673 patent, prior to the expiration of the '673 patent, including any extensions to which Plaintiff is or becomes entitled;

G. An Order be issued that Defendants Reddy Ltd., Reddy Inc., Roxane, Cobalt Labs, Cobalt Pharma, Glenmark USA, Glenmark Ltd., Glenmark Pharma, Orchid Healthcare, Orchid Ltd., Orgenus, Lupin Pharma, Lupin Ltd., Sun Global, Sun Pharma

Inc., Sun Pharma Ltd., Alphapharm Ltd. and Mylan Inc., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing or selling the proposed generic versions of Sepracor's Lunesta[®] brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '926 and '724 patents, prior to the expiration of the '926 and '724 patents, including any extensions to which Plaintiff is or becomes entitled;

H. Sepracor be awarded monetary relief if any Defendant commercially manufactures, uses, offers for sale, or sells a generic version of Sepracor's Lunesta[®] brand product, or any other product that infringes or induces or contributes to the infringement of the '257, '673, '926 or '724 patent, within the United States prior to the expiration of those patents, including any extensions, and that any such monetary relief be awarded to Sepracor with prejudgment interest;

I. A Judgment be entered against each Defendant that this case is exceptional and that Sepracor is entitled to its reasonable attorney fees, costs and expenses that it incurs prosecuting this action as to that Defendant; and

J. Sepracor be awarded such other and further relief as this Court
deems just and proper.

Dated: March 20, 2009

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza
Newark, New Jersey 07102-5490
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff Sepracor Inc.

Of Counsel:
Joseph M. O'Malley, Jr.
Bruce M. Wexler
David M. Conca
Eric W. Dittmann
PAUL, HASTINGS, JANOFSKY
& WALKER LLP
75 East 55th Street
New York, NY 10022
(212) 318-6000

LOCAL CIVIL RULE 11.2 CERTIFICATION

I hereby certify that the matter in controversy is not the subject of any other action pending in any court, or any pending arbitration or administrative proceeding.

Dated: March 20, 2009

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza
Newark, New Jersey 07102-5490
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff Sepracor Inc.

Of Counsel:
Joseph M. O'Malley, Jr.
Bruce M. Wexler
David M. Conca
Eric W. Dittmann
PAUL, HASTINGS, JANOFSKY
& WALKER LLP
75 East 55th Street
New York, NY 10022
(212) 318-6000

EXHIBIT A

US006864257B2

(12) **United States Patent**
Cotrel et al.(10) **Patent No.:** **US 6,864,257 B2**
(45) **Date of Patent:** **Mar. 8, 2005**(54) **OPTICALLY ACTIVE 5H-PYRROLO[3,4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**(75) Inventors: **Claude Cotrel**, Paris (FR); **G rard Roussel**, Soisy sur Seine (FR)(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 227 days.

(21) Appl. No.: **10/200,510**(22) Filed: **Jul. 23, 2002**(65) **Prior Publication Data**

US 2002/0193378 A1 Dec. 19, 2002

Related U.S. Application Data

(62) Division of application No. 09/722,438, filed on Nov. 28, 2000, now Pat. No. 6,444,673, which is a continuation of application No. 09/124,651, filed on Jul. 29, 1998, now Pat. No. 6,319,926, which is a continuation of application No. 08/493,946, filed on Jun. 23, 1995, now abandoned, which is a continuation of application No. 08/342,794, filed on Nov. 21, 1994, now abandoned, which is a continuation of application No. 08/232,313, filed on Apr. 25, 1994, now abandoned, which is a continuation of application No. 08/109,863, filed on Aug. 20, 1993, now abandoned, which is a continuation of application No. 08/034,199, filed on Mar. 19, 1993, now abandoned, which is a continuation of application No. 07/821,662, filed on Jan. 16, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Jan. 17, 1991 (FR) 91 00490

(51) **Int. Cl.**⁷ **C07D 487/04**; A61K 31/4985; A61P 25/20(52) **U.S. Cl.** **514/249**(58) **Field of Search** 514/249(56) **References Cited****U.S. PATENT DOCUMENTS**

3,862,149 A	1/1975	Cotrel et al.	260/268.32
4,220,646 A	9/1980	Cotrel et al.	424/250
4,868,214 A	9/1989	Sunshine et al.	
4,962,124 A	10/1990	Sunshine et al.	514/568
5,102,890 A	4/1992	Bourzat et al.	514/294
5,331,000 A	7/1994	Young et al.	514/570
5,786,357 A	7/1998	Young et al.	
6,319,926 B1	11/2001	Cotrel et al.	
6,436,936 B1 *	8/2002	Young et al.	514/249

FOREIGN PATENT DOCUMENTS

EP	0 495 717	7/1992
WO	WO 93/10788	6/1993

OTHER PUBLICATIONSH. Tamura, et al, "Chronic Oral Toxicity Study of Zopiclone (27 267 RP) in Beagle dogs for 6 Months and Recovery Testing After Treatment," *Pharmacometrics*, 26(6): 969-1003 (1983).*

Unpublished summary data sheet from IND Serial No. 000, (s)-zopiclone, owned by assignee Sepracor Inc., p. 8-108 (1 page total).*

Nair N.P.V., Schwartz G., Dimitri R. et al. A dose-range finding study of zopiclone in insomniac patients. *Intl Clin Psychopharmacol* 1990; 5 (Suppl 2): 1-10.Martindale. The Extra Pharmacopoeia. The Royal Pharmaceutical Society, London 1996; 31st edition: pp. 743-744.Houghton G. W., Dennis M.J., Templeton R., Martin B.K. A repeated dose pharmacokinetic study of a new hypnotic agent, zopiclone (Imovane®). *Intl J Clin Pharmacol Therap Toxicol* 1985, 23: 97-100.Marc-Aur le J., Caille G., Bourgoin J. Comparison of zopiclone pharmacokinetics in patients with impaired renal function and normal subjects. Effects of hemodialysis. *Sleep* 1987; 10(Suppl 1): 22-26.Parker G., Roberts C.J.C.. Plasmas concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; 16:259-265.Viron B., De Meyer M., Le L'iboux A. et al., Steady-state pharmacokinetic of zopiclone during multiple oral dosing (7.5 mg nocte) in patients with severe chronic renal failure. *Intl Clin Psychopharmacol* 1990; 5 (Suppl 2): 95-104.Sikdar S., Ruben S.M., Zopiclone abuse among polydrug users. *Addiction* 1996; 91: 285-286.Noble S., Langtry H.D., Lamb H.M., Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of Insomnia. *Drugs* 198; 55:277-302.Fernandez C., Martin C., Gimenez F., Farinotti. Clinical pharmacokinetics of zopiclone, *Clin Pharmacokinet* 1995; 29: 431-441.Le Liboux Z., Frydman A., Gaillot J., Simultaneous Determination of Zopiclone and Its Two Major Metabolites (N-Oxide and N-Desmethyl) in Human Biological Fluids by Reversed-Phase High-Performance Liquid Chromatography, *J. Chromatography*, 417: (1987) 151-158.Musch B. and Maillard F., Zopiclone, The Third Generation Hypnotic: a Clinical Overview, *Intl. Clin. Psychopharmacol.* 5:147-58 (1990).Julou L., Blanchard J.C., and Dreyfus J.F., Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone, *Pharmacol., Biochem. & Beh.*, 23: 653-659 (1985).Broadhurst A. and Cushnaghan R.C., Residual effects of Zopiclone (Imovane), *Sleep*, 10 (Suppl. 1): 48-53 (1987).

(List continued on next page.)

Primary Examiner—Mark L. Berch(74) **Attorney, Agent, or Firm**—Heslin Rothenberg Farley & Mesiti P.C.(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquilisers and hypnotics.

7 Claims, No Drawings

US 6,864,257 B2

Page 2

OTHER PUBLICATIONS

- Anderson A., Zopiclone and Nitrazepam: A Multicenter Placebo Controlled Comparative Study of Efficacy and Tolerance In Insomniac Patients in General Practice, *Sleep*, 10 (Suppl. 1): 54–62 (1987).
- Tamminen T. and Hensen P.P., Chronic Administration of Zopiclone and Nitrazepam in the Treatment of Insomnia, *Sleep*, 10 (Suppl. 1): 63–72 (1987).
- Inman W., Kubota K., Pearce G., Wilton W., PEM Report No. 10. Zopiclone, *Pharmacoepidemiol Drug Safety* 1993; 2: 499–521.
- Doble A., Canton T., Malgouris C., et al. The mechanism of action of zopiclone. *Eur Psychiat* 1995; 10 (Suppl 3): 117s–128s.
- Karle J. and Nielsen M., The Mechanism of Action and Pharmacology of Zopiclone, Rev. Contemp. Pharmacother., vol. 9, No. 2, pp. 77–87 (1998).
- Richards G., Schoch P., Haefely W., Benzodiazepine receptors: new vistas. *Sem Neurosci* 1991; 3: 191–203.
- Doble A., Martin I.L., *The GABA_A/benzodiazepine receptor as a target for psychoactive drugs*, RG Landes Company, Austin 1996; pp. 229–264.
- Langtry H.D., Benfield P., Zolpidem: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential, *Drugs*, 1990; 40: 291–313.
- Blanchard J.C., Boireau A., Garret C., Julou L. In vitro and in vivo Inhibition by zopiclone of benzodiazepine binding to rodent brain receptors. *Life Sci* 1979; 24: 2417–2420.
- Möhler H., Okada T. The benzodiazepine receptor in normal and pathological human brain. *Brit J Psychiat* 1978; 133: 261–268.
- Gaillot J., Le Roux Y., Houghton G.W., Dreyfus J.F. Critical factors for pharmacokinetics of zopiclone in the elderly and in patients with liver and renal Insufficiency. *Sleep* 1987; 10 (Suppl 1): 7–21.
- Doble et al., “The Pharmacology of Cyclopyrrolone Derivatives Acting at the GABA_A/Benzodiazepine Receptor,” *Adv. Biochem. Psychopharmacol.*, 47:407–418 (1992).
- Gaillot et al., “Pharmacokinetics and Metabolism of Zopiclone,” *Int. Pharmacophysiol.* 17:suppl. 2, pp. 76–91 (1982)/*Pharmacology* 27:suppl. 2, pp. 76–91 (1983).
- E.J. Ariens, “Stereoselectivity in Pharmacodynamics and Pharmacokinetics,” *Schweiz. Med. Wschr.* 120:131–134 (1990).
- Dragstedt, C.A. and Lang, V.F., “Respiratory Stimulants In Acute Cocaine Poisoning In Rabbits,” *J. Pharmacol. Ex. Ther.* 32:215–222 (1928).
- Utchfield, J.T., Jr., and Wilcoxon, F., “A Simplified Method of Evaluating Dose–Effect Experiments,” *J. Pharmacol. and Exp. Therap.* 96:99–113 (1949).
- Casarett and Douil’s Toxicology: The Basic Science of Poisons, 5th ed. (1996) pp. 21–23.
- Prieur, David J. et al., “Procedures for Preclinical Toxicologic Evaluation of Cancer Chemotherapeutic Agents: Protocols of the Laboratory of Toxicology,” *Cancer Chemotherapy Reports*, Jan. 1973, part 3, vol. 4, No. 1:1–30.
- Everett et al., “Comparative Anticonvulsive Action of 3,5,5-Trimethyloxazolidine-2,4-Dione (Tridone), Dilantin and Phenobarbital,” *J. Pharmacol.* 81:402 (1944).
- Schwinn et al., “Functional Effects of Activation of Alpha-1 Adrenoceptors by Dexmedetomidine: In Vivo and In Vitro Studies,” *J. Pharmacol. & Exp. Therap.*, 259 (1991).
- Marley et al., “Differential Response to Flurazepam In Long–Sleep and Short–Sleep Mice,” *Pharmacol, Biochem. & Behav.*, 31:453–58 (1987).
- G. Zbinden et al., “Pharmacology of Benzodiazepines: Laboratory and Clinical Correlations,” *Advances in Pharmacology*, 5:213–291 (1967).
- W.H. DeCamp, “The FDA Perspective on the Development of Stereoisomers,” *Chirality*, 1:2–6 (1989).
- D.J. Birkett, “Racemates or Enantiomers: Regulatory Approaches,” *Clinical and Experimental Pharmacology & Physiology*, 16:479–483 (1989).
- R.F. Squires et al., “Benzodiazepine Receptors in Rat Brain,” *Nature*, 266:732–734 (1977).
- R.E. Study et al., “Cellular Mechanisms of Benzodiazepine Action,” *JAMA*, 247:2137–2151 (1982).
- D. Nutt, “Selective Ligands for Benzodiazepine Receptors: Recent Developments,” *Curr. Aspects Neurosci.*, 2:259–293 (1990).
- G. Richards et al., “Role of GABA in the mechanism of benzodiazepine action,” *Seminars in Neurosciences*, 3:191–203 (1991).
- J.T. Litchfield, “A Method for Rapid Graphic Solution of Time–Percent Effect Curves,” *J. Pharmacol. and Exp. Therap.*, 97:399–408 (1949).
- G.W. Snedecor et al., *Statistical Methods*, 7th ed., 149.
- Fiche Technique No. 6, *J. Pharmacol. and Experim. Therap.*, 3:407–914 (1970).
- E.J. Ariens, “Racemic therapeutics—ethical and regulatory aspects,” *Eur. J. Clin. Pharmacol.* 41:89–93 (1991).
- C. Fernandez et al., “Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbonate column,” *J. Chromatog.*, 572:195–202 (1991).
- P. Gauthier et al., “Influence of Zopiclone, a New Generation Hypnotic, on the Intermediate Stage and Paradoxical Sleep in the Rat,” *Psychopharmacol.*, 130:139–143 (1997).
- Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 8th ed. 346–349 (1990).
- C. Malgouris et al., “Autoradiographic Distribution of (3H)–Suridone Binding Sites in the Rat Brain,” *Drug Develop. Res.*, 34:336–343 (1995).
- A. Doble et al., “The mechanism of action of zopiclone,” *Eur. Psychiatry*, 10 Suppl. 3:117s–128s (1995).
- J.M. Stutzmann et al., “Pharmacological Properties and Mechanism of Action of the Cyclopyrrolones,” *L. Encéphale*, XVIII:393–400 (1992).
- V. Bertolasi et al., “Stereochemistry of Benzodiazepine Receptor Ligands. Possible Role of C–H . . . X Interactions in Drug–Receptor Binding and Crystal Structures of CL 218–872, Zopiclone and DMCM,” *J. Chem. Soc. Perkin Trans.*, 2:283–289 (1990).
- F. Jamali et al., “Enantioselective Aspects of Drug Action and Disposition: Therapeutic Pitfalls,” *Journal of Pharmaceutical Sciences*, 78(9):695–715 (1989).
- A. Verma and S.H. Snyder, “Peripheral Type Benzodiazepine Receptors”, *Annu. Rev. Pharmacol. Toxicol.*, 29:307–322 (1989).
- J.P. Brun, “Zopiclone, a Cyclopyrrolone Hypnotic: Review of Properties,” *Pharmacology, Biochemistry and Behavior*, 29:831–832 (1988).
- P.A. Borea et al., “Stereochemical Features Controlling Binding and Intrinsic Activity Properties of Benzodiazepine–Receptor Ligands”, *Molecular Pharmacology*, 31:334–344 (1987).

US 6,864,257 B2

Page 2

- K.L. Goa and R.C. Heel, "Zopiclone, a Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy as an Hypnotic," *Drugs*, 32(1):48-65 (1986).
- P. Jacqmin and M. Lesne, "Les Benzodiazepines: Aspects Pharmacodynamiques," *J. Pharm. Belg.*, 40(1):35-54 (1985).
- L. Julou et al., "Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone," *Pharmacology, Biochemistry and Behavior*, 23:653-659 (1985).
- H. Kusnierczyk, "Antitumor Activity of Optical Isomers of Cyclophosphamide, Ifosfamide and Trofosfamide as Compared to Clinically Used Racemates," *J. Immunopharm.*, 8(4):455-480 (1986).
- F. Jamali, "Pharmacokinetics of enantiomers of chiral non-steroidal anti-inflammatory drugs," *Eur. J. Drug Metab. and Pharmacokin*, 12(1):1-9 (1988).
- D.W. Robertson et al., "Absolute Configurations and Pharmacological Activities of the Optical Isomers of Fluoxetine & Selective Serotonin-Uptake Inhibitor," *J. Med. Chem.*, 31:1412-1417 (1988).
- Braestrup C., Squires R.F. Brain specific benzodiazepine receptors. *Brit J Psychiat* 1978; 133: 249-260.
- Garzone P., Kroboth P., Pharmacokinetics of the Newer Benzodiazepines, *Clinical Pharmacokinetics* 16: 337-364 (1989).
- Miller L.G., Galpem W.R., Byrnes J.J., and Greenblatt, D.J., Benzodiazepine Receptor Binding of Benzodiazepine Hypnotics: Receptor and Ligand Specificity, *Pharmacology Biochem. And Beh.* vol. 43, pp. 413-416, 1992.
- Greenblatt D.J., Divoll M., Abernethy D.R., Ochs H.R., and Shader R.I., Clinical Pharmacokinetics of the Newer Benzodiazepines, *Clin Pharmacokinetics*, 8: 233-252 (1983).
- Benavides, J., Peny B., Durand A. et al. Comparative in vivo and in vitro regional selectivity of central ω (benzodiazepine) site ligands in inhibiting [3 H]flumazenil binding in the rat central nervous system. *J Pharmacol Exp Therap* 1992; 263: 884-896.
- Ankier S.I., Goa K.L., Quazepam: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Insomnia, *Drugs* 35: 42-62 (1988).
- Gaillot J., Heusse D., Houghton G.W. et al. Pharmacokinetics and metabolism of zopiclone, *Int. Pharmacopsychiat* 1983; 17 (Suppl 2): 76-91.

* cited by examiner

US 6,864,257 B2

1

**OPTICALLY ACTIVE 5H-PYRROLO[3,4-B]
PYRAZINE DERIVATIVE, ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

This is a divisional of Application Ser. No. 09/722,438, filed Nov. 28, 2000, now U.S. Pat. No. 6,444,673 which is a continuation of Application Ser. No. 09/124,651, filed Jul. 29, 1998, now U.S. Pat. No. 6,319,926, which is a continuation of Application Ser. No. 08/493,946, filed Jun. 3, 1995 (abandoned), which is a continuation of Application Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of Application Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of Application Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of Application Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of Application Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned), the disclosures of which are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo[3,4-b]-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD₅₀) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD₅₀ of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, *J. of Neurochemistry*, 40, 601 (1983) based on the work of Squires and Braestrup, *Nature*, 266, 732-734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, *J. Pharmacol.*, 81, 402

2

(1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, *Advances in Pharmacology* 5, 213-291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitriles such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnotic, sedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis (β -hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and

US 6,864,257 B2

3

injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46% yield, a crystallised product (21.3 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}=83^\circ$ (c=0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}=102^\circ$ (c=0.5; acetone), is thereby obtained in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}=135^\circ\pm 3^\circ$ (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}=-21^\circ$ (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous

4

phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}=-133^\circ\pm 3^\circ$ (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

dextrorotatory isomer of zopiclone	0.003 g
starch	0.100 g
precipitated silica	0.035 g
magnesium stearate	0.005 g

What is claimed is:

1. A method of inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquilizing effect, in a human in need of said induction, comprising administering to the human an effective quantity of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer.

2. The method according to claim 1, wherein said administering step comprises administering a pharmaceutical composition comprising an effective amount of said 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer, and a pharmaceutically acceptable carrier.

3. The method according to claim 1, wherein the pharmaceutically acceptable salt is a salt of a mineral acid, or a substituted derivative thereof, selected from the group consisting of hydrochlorides, sulfates, nitrates, and phosphates.

4. The method according to claim 1, wherein the pharmaceutically acceptable salt is a salt of an organic acid, or a substituted derivative thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, and phenolphthalinates.

5. The method according to claim 1, wherein the effective quantity is from about 2.5 mg to about 15 mg per day.

6. The method according to claim 2, wherein the pharmaceutically acceptable carrier comprises a diluent.

7. The method according to claim 2 wherein the composition is administered orally, rectally or parenterally.

* * * * *

EXHIBIT B

(12) **United States Patent**
Cotrel et al.

(10) **Patent No.: US 6,444,673 B1**
(45) **Date of Patent: Sep. 3, 2002**

- (54) **OPTICALLY ACTIVE 5H-PYRROLO[3,4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**
- (75) Inventors: **Claude Cotrel**, Paris; **G rard Roussel**, Soisy sur Seine, both of (FR)
- (73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) Appl. No.: **09/722,438**
- (22) Filed: **Nov. 28, 2000**

Related U.S. Application Data

- (63) Continuation of application No. 09/124,651, filed on Jul. 29, 1998, which is a continuation of application No. 08/493,946, filed on Jun. 23, 1995, now abandoned, which is a continuation of application No. 08/342,794, filed on Nov. 21, 1994, now abandoned, which is a continuation of application No. 08/232,313, filed on Apr. 25, 1994, now abandoned, which is a continuation of application No. 08/109,863, filed on Aug. 20, 1993, now abandoned, which is a continuation of application No. 08/034,199, filed on Mar. 19, 1993, now abandoned, which is a continuation of application No. 07/821,662, filed on Jan. 16, 1992, now abandoned.
- (30) **Foreign Application Priority Data**
Jan. 17, 1991 (FR) 91 00490
- (51) **Int. Cl.**⁷ **C07D 487/04**; A61P 25/20; A61K 31/4985
- (52) **U.S. Cl.** **514/249**; 540/350
- (58) **Field of Search** 544/350; 514/249

References Cited

U.S. PATENT DOCUMENTS			
3,862,149	A	1/1975	Cotrel et al. 260/268
4,220,646	A	9/1980	Catrel et al. 424/250
4,868,214	A	9/1989	Sunshine et al. 514/568
4,962,124	A	10/1990	Sunshine et al. 514/568
5,102,890	A	4/1992	Bourzat et al. 514/299
5,331,000	A *	7/1994	Young et al. 514/570
5,786,357	A	7/1998	Young et al. 514/249

FOREIGN PATENT DOCUMENTS

EP	0 495 717	7/1992
WO	WO 93/10788	6/1993

OTHER PUBLICATIONS

H. Tamura, et al, "Chronic Oral Toxicity Study of Zopiclone (27 267 RP) in Beagle Dogs for 6 Months and Recovery Testing After Treatment," *Pharmacometrics*, 26(6): 969-1003 (1983).
Unpublished summary data sheet from IND Serial No. 000, (s)-zopiclone, owned by assignee Sepracor Inc., p. 8-108 (1 page total).
Nair N.P.V., Schwartz G., Dimitri R. et al. A dose-range finding study of zopiclone in insomniac patients. *Intl Clin Psychopharmacol* 1990; 5 (Suppl 2): 1-10.

Martindale. The Extra Pharmacopoeia. The Royal Pharmaceutical Society, London 1996; 31st edition: pp. 743-744.
Houghton G.W., Dennis M.J., Templeton R., Martin B.K.. A repeated dose pharmacokinetic study of a new hypnotic agent, zopiclone (Imovane ). *Intl J Clin Pharmacol Therap Toxicol* 1985; 23: 97-100.
Marc-Aur le J., Caille G., Bourgoin J. Comparison of zopiclone pharmacokinetics in patients with impaired renal function and normal subjects. Effects of hemodialysis. *Sleep* 1987; 10 (Suppl 1): 22-26.
Parker G., Roberts C.J.C.. Plasmas concentrations and central nervous sytem effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; 16:259-265.
Viron B., De Meyer M., Le Liboux A. et al., Steady-state pharmacokinetic of zopiclone during multiple oral dosing (7.5 mg nocte) in patients with severe chronic renal failure. *Intl Clin Pysychopharmacol* 1990; 5 (Suppl 2): 95-104.
Sikdar S., Ruben S.M., Zopiclone abuse among polydrug users. *Addition* 1996; 91: 285-286.
Noble S., Langtry H.D., Lamb H.M., Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 198; 55:277-302.
Fernandez C., Martin C., Gimenez F., Farinotti. Clinical pharmacokinetics of zopiclone, *Clin Pharmacokinet* 1995; 29: 431-441.
Le Liboux Z., Frydman A., Gaillot J., Simultaneous Determination of Zopiclone and Its Two Major Metabolites (N-Oxide and N-Desmethyl) in Human Biological Fluids by Reversed-Phase High-Performance Liquid Chromatography, *J. Chromatography*, 417: (1987) 151-158.
Musch B. and Maillard F., Zopiclone, The Third Generation Hypnotic: a Clinical Overview, *Intl. Clin. Psychopharmacol.* 5: 147-58 (1990).
Julou L., Blanchard J.C., and Dreyfus J.F., Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone, *Pharmacol., Biochem. & Beh.*, 23: 653-659 (1985).
Broadhurst A. and Cushnaghan R.C., Residual effects of Zopiclone (Imovane), *Sleep*, 10 (Suppl. 1): 48-53 (1987).
Anderson A., Zopiclone and Nitrazepam: A Mutlicenter Placebo Controlled Comparative Study of Efficacy and Tolerance in Insomniac Patients in General Practice, *Sleep*, 10 (Suppl. 1): 54-62 (1987).
Tamminen T. and Hensen P.P., Chronic Administration of Zopiclone and Nitrazepam in the Treatment of Insomnia, *Sleep*, 10 (Suppl. 1): 63-72 (1987).
Inman W., Kubota K., Pearce G., Wilton W., PEM Report No. 10. Zopiclone, *Pharmacoepidemiol Drug Safety* 1993; 2: 499-521.

(List continued on next page.)

Primary Examiner—Mark L Berch
(74) *Attorney, Agent, or Firm*—Sughrue Mion, PLLC

(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquilizers and hypnotics.

8 Claims, No Drawings

OTHER PUBLICATIONS

- Doble A., Canton T., Malgouris C., et al. The mechanism of action of zopiclone. *Eur Psychiat* 1995; 10 (Suppl 3): 117s–128s.
- Karle J. and Nielsen M., The Mechanism of Action and Pharmacology of Zopiclone, Rev. Contemp. Pharmacother., vol. 9, No. 2, pp. 77–87 (1998).
- Richards G., Schoch P., Haefely W., Benzodiazepine receptors: new vistas. *Sem Neurosci* 1991; 3: 191–203.
- Doble A., Martin I.L., *The GABA_A/benzodiazepine receptor as a target for psychoactive drugs*. RG Landes Company, Austin 1996; pp. 229–264.
- Langtry H.D., Benfield P., Zolpidem: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential, *Drugs*, 1990; 40: 291–313.
- Blanchard J.C., Boireau A., Garret C., Julou L. In vitro and in vivo inhibition by zopiclone of benzodiazepine binding to rodent brain receptors. *Life Sci* 1979; 24: 2417–2420.
- Möhler H., Okada T. The benzodiazepine receptor in normal and pathological human brain. *Brit J Psychiat* 1978; 133: 261–268.
- Gaillot J., Le Roux Y., Houghton G.W., Dreyfus J.F., Critical factors for pharmacokinetics of zopiclone in the elderly and in patients with liver and renal insufficiency. *Sleep* 1987; 10 (Suppl 1): 7–21.
- Doble et al., “The Pharmacology of Cyclopyrrolone Derivatives Acting at the GABA_A/Benzodiazepine Receptor,” *Adv. Biochem. Psychopharmacol.*, 47:407–418 (1992).
- Gaillot et al., “Pharmacokinetics and Metabolism of Zopiclone,” *Int. Pharmacophysiol.* 17:suppl. 2, pp. 76–91 (1982)/*Pharmacology* 27:suppl. 2, pp. 76–91 (1983).
- E.J. Ariens, “Stereoselectivity in Pharmacodynamics and Pharmacokinetics,” *Schweiz. Med. Wschr.* 120:131–134 (1990).
- Dragstedt, C.A. and Lang, V.F., “Respiratory Stimulants In Acute Cocaine Poisoning in Rabbits,” *J. Pharmacol. Ex. Ther.* 32:215–222 (1928).
- Litchfield, J.T., Jr., and Wilcoxon, F., “A Simplified Method of Evaluating Dose–Effect Experiments,” *J. Pharmacol. and Exp. Therap.* 96:99–113 (1949).
- Casarett and Doull’s Toxicology: The Basic Science of Poisons, 5th ed. (1996) pp. 21–23.
- Prieur, David J. et al., “Procedures for Preclinical Toxicology Evaluation of Cancer Chemotherapeutic Agents: Protocols of the Laboratory of Toxicology,” *Cancer Chemotherapy Reports*, Jan. 1973, part 3, vol. 4, No. 1:1–30.
- Everett et al., “Comparative Anticonvulsive Action of 3,5, 5–Trimethyloxazolidine–2,4–Dione (Tridone), Dilantin and Phenobarbital,” *J. Pharmacol.* 81:402 (1944).
- Schwinn et al., “Functional Effects of Activation of Alpha–1 Adrenoceptors by Dexmedetomidine: In Vivo and In Vivo Studies,” *J. Pharmacol. & Exp. Therap.*, 259 (1991).
- Marley et al., “Differential Response to Flurazepam in Long–Sleep and Short–Sleep Mice,” *Pharmacol, Biochem. & Behav.*, 31:453–58 (1987).
- G. Zbinden et al., “Pharmacology of Benzodiazepines: Laboratory and Clinical Correlations,” *Advances in Pharmacology*, 5:213–291 (1967).
- W.H. DeCamp, “The FDA Perspective on the Development of Stereoisomers,” *Chirality*, 1:2–6 (1989).
- D.J. Birkett, “Racemates or Enantiomers: Regulatory Approaches,” *Clinical and Experimental Pharmacology & Physiology*, 16:479–483 (1989).
- R.F. Squires et al., “Benzodiazepine Receptors in Rat Brain,” *Nature*, 266:732–734 (1977).
- R.E. Study et al., “Cellular Mechanisms of Benzodiazepine Action,” *JAMA*, 247:2147–2151 (1982).
- D. Nutt, “Selective Ligands for Benzodiazepine Receptors: Recent Developments,” *Curr. Aspects Neurosci.*, 2:259–293 (1990).
- G. Richards et al., “Role of GABA in the mechanism of benzodiazepine action,” *Seminars in Neurosciences*, 3:191–203 (1991).*
- J.T. Litchfield, “A Method for Rapid Graphic Solution of Time–Percent Effect Curves,” *J. Pharmacol. and Exp. Therap.*, 97:399–408 (1949).*
- G.W. Snedecor et al., Statistical Methods, 7th ed., 149.*
- Fiche Technique No. 6, J. Pharmacol. and Experim. Therap., 3:407–914 (1970).*
- E.J. Ariens, “Racemic Therapeutics—ethical and regulatory aspects,” *Eur. J. Clin. Pharmacol.* 41:89–93 (1991).*
- C. Fernandez et al., “Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbonate column,” *J. Chromatog.*, 572:195–202 (1991).*
- P. Gauthier et al., “Influence of Zopiclone, a New Generation Hypnotic, on the Intermediate Stage and Paradoxical Sleep in the Rat,” *Psychopharmacol.*, 130:139–143 (1997).*
- Goodman & Gilman’s, The Pharmacological Basis of Therapeutics, 8th ed. 346–349 (1990).*
- C. Malgouris et al., “Autoradiographic Distribution of [3H]–Suridone Binding Sites in the Rat Brain,” *Drug Develop. Res.*, 34:336–343 (1995).
- A. Doble et al., “The mechanism of action of zopiclone,” *Eur. Psychiatry*, 10 Suppl. 3:117s–128s (1995).
- J.M. Stutzmann et al., “Pharmacological Properties and Mechanism of Action of the Cyclopyrrolones,” *L’Encéphale*, XVIII:393–400 (1992).
- V. Bertolasi et al., “Stereochemistry of Benzodiazepine Receptor Ligands. Possible Role of C–H . . . X Interactions in Drug–Receptor Binding and Crystal Structures of CL 218–872, Zopiclone and DMCM,” *J. Chem. Soc. Perkin Trans.*, 2:283–289 (1990).
- F. Jamali et al., “Enantioselective Aspects of Drug Action and Disposition: Therapeutic Pitfalls,” *Journal of Pharmaceutical Sciences*, 78(9):695–715 (1989).
- A. Verma and S.H. Snyder, “Peripheral Type Benzodiazepine Receptors,” *Annu. Rev. Pharmacol. Toxicol.*, 29:307–322 (1989).
- J.P. Brun, “Zopiclone, a Cyclopyrrolone Hypnotic: Review of Properties,” *Pharmacology, Biochemistry and Behavior*, 29:831–832 (1988).
- P.A. Borea et al., “Stereochemical Features Controlling Binding and Intrinsic Activity Properties of Benzodiazepine–Receptor Ligands,” *Molecular Pharmacology*, 31:334–344 (1987).
- K.L. Goa and R.C. Heel, “Zopiclone, a Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy as an Hypnotic,” *Drugs*, 32(1):48–65 (1986).
- P. Jacqmin and M. Lesne, “Les Benzodiazepines: Aspects Pharmacodynamiques,” *J. Pharm. Belg.*, 40(1):35–54 (1985).
- L. Julou et al., “Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone,” *Pharmacology, Biochemistry and Behavior*, 23:653–659 (1985).

US 6,444,673 B1

Page 3

- H. Kusnierczyk, "Antitumor Activity of Optical Isomers of Cyclophosphamide, Ifosfamide and Trofosfamide as Compared to Clinically Used Racemates," *J. Immunopharm.*, 8(4):455-480 (1986).
- F. Jamali, "Pharmacokinetics of enantiomers of chiral non-steroidal anti-inflammatory drugs," *Eur. J. Drug Metab. and Pharmacokin.*, 12(1):1-9 (1988).
- D.W. Robertson et al., "Absolute Configurations and Pharmacological Activities of the Optical Isomers of Fluoxetine & Selective Serotonin-Uptake Inhibitor," *J. Med. Chem.*, 31:1412-1417 (1988).
- Braestrup C., Squires R.F.. Brain specific benzodiazepine receptors. *Brit J Psychiat* 1978; 133: 249-260.
- Garzone P., Kroboth P., Pharmacokinetics of the Newer Benzodiazepines, *Clinical Pharmacokinetics* 16: 337-364 (1989).
- Miller L.G., Galpern W.R., Byrnes J.J., and Greenblatt, D.J., Benzodiazepine Receptor Binding of Benzodiazepine Hypnotics: Receptor and Ligand Specificity, *Pharmacology Biochem. And Beh.* vol. 43, pp. 413-416, 1992.
- Greenblatt D.J., Divoll M., Abernethy D.R., Ochs H.R., and Shader R.I., Clinical Pharmacokinetics of the Newer Benzodiazepines, *Clin Pharmacokinetics*, 8: 233-252 (1983).
- Benavides, J., Peny B., Durand A. et al. Comparative in vivo and in vitro regional selectivity of central ω (benzodiazepine) site ligands in inhibiting [^3H]flumazenil binding in the rat central nervous system. *J Pharmacol Exp Therap* 1992; 263: 884-896.
- Ankier S.I., Goa K.L., Quazepam: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Insomnia, *Drugs* 35: 42-62 (1988).
- Gaillot J., Heusse D., Houghton G.W. et al. Pharmacokinetics and metabolism of zopiclone. *Int Pharmacopsychiat* 1983; 17 (Suppl 2): 76-91.

* cited by examiner

US 6,444,673 B1

1

**OPTICALLY ACTIVE 5H-PYRROLO[3,4-B]
PYRAZINE DERIVATIVE, ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

This is a continuation of application Ser. No. 09/124,651, filed Jul. 29, 1998, which is a continuation of Ser. No. 08/493,946, filed Jun. 23, 1995 (abandoned), which is a continuation of Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned), the disclosure of which is incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo(3,4-b)-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD₅₀) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD₅₀ of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, *J. of Neurochemistry*, 40, 601 (1983) based on the work of Squires and Braestrup, *Nature*, 266, 732-734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, *J. Pharmacol.*, 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, *Advances in Pharmacology* 5, 213-291 (1967), the dextrorotatory isomer is approxi-

2

mately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitriles such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis(β-hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation

US 6,444,673 B1

3

may be carried out in several ways, e.g. using a bacterio-
logical filter, by incorporating sterilising agents in the
composition, by irradiation or by heating. They may be
prepared. in the form of sterile compositions which can be
dissolved at the time of use in sterile water or any other
sterile injectable medium.

The compositions for rectal administration are supposi-
tories which can contain, apart from the active product,
excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought
and the treatment period; taken orally, they are generally
between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied
limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichlo-
romethane (300 cc) is added to a solution of D(+)-O,O'-
dibenzoyltartaric acid in the form of a monohydrate (22.56
g; 0.06 mol) in dichloromethane (300 cc). The reaction
mixture is concentrated to dryness under reduced pressure.
The crude salt obtained is recrystallised in acetonitrile (2000
cc) to give, in a 46% yield, a crystallised product (21.3 g),
m.p. 160–165° C. (with decomposition), the optical rotation
of which is $[\alpha]_D^{20}=83^\circ$ (c=0.5; acetone).

The product obtained is dissolved in dichloromethane
(180 cc) under reflux. Acetonitrile (200 cc) is added and the
mixture is left standing for 1 hour at a temperature of 5° C.
The crystallised product obtained is recrystallised again
under the same conditions. A crystallised salt (16.5 g), m.p.
160–165° C. (with decomposition), the optical rotation
of which is $[\alpha]_D^{20}=102^\circ$ (c=0.5; acetone), is thereby obtained
in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in
the presence of dichloromethane (125 cc). The mixture is
alkalinised to pH 11 by slowly adding 2N aqueous sodium
hydroxide solution. After settling has taken place, the aque-
ous phase is separated and extracted twice with dichlo-
romethane. The combined organic phases are washed with
water and then dried over magnesium sulphate. After
filtration, evaporation of the solvent and recrystallisation of
the product obtained in acetonitrile (80 cc), the dextrorota-
tory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical
rotation of which is $[\alpha]_D^{20}=135^\circ\pm3^\circ$ (c=1.0; acetone), is
obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopi-
clone with D(+)-O,O'-dibenzoyltartaric acid are concen-
trated to dryness under reduced pressure to give a salt (22.05
g) the optical rotation of which is $[\alpha]_D^{20}=-21^\circ$ (c=0.2;
acetone).

The salt thereby obtained is dissolved in water (125 cc) in
the presence of dichloromethane (125 cc). The mixture is
alkalinised to pH 11 by slowly adding 2N aqueous sodium
hydroxide solution. After settling has taken place, the aque-
ous phase is separated and extracted twice with dichlo-
romethane. The combined organic phases are washed with
water and then dried over magnesium sulphate. After filtra-
tion and evaporation of the solvent, the crystallised solid
obtained (8.45 g) is recrystallised in acetonitrile
(successively 100, 50 and 45 cc). The laevorotatory isomer

4

(3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of
which is $[\alpha]_D^{20}=-133^\circ\pm3^\circ$ (c=1.0; acetone), is thereby
obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the
following composition are prepared according to the usual
technique:

dextrorotatory isomer of zopiclone	0.003 g
starch	0.100 g
precipitated silica	0.035 g
magnesium stearate	0.005 g

What is claimed is:

1. 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)
carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]
pyrazine, or a pharmaceutically acceptable salt thereof, in
the form of its dextrorotatory isomer and essentially free of
its levorotatory isomer.

2. A pharmaceutical composition comprising an effective
amount of the dextrorotatory isomer, essentially free of the
levorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-
1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo
[3,4-b]pyrazine, or a pharmaceutically acceptable salt
thereof, and a pharmaceutically acceptable carrier.

3. The compound according to claim 1, wherein the
pharmaceutically acceptable salt is a salt of a mineral acid,
or a substituted derivative thereof, selected from the group
consisting of hydrochlorides, sulfates, nitrates, and phos-
phates.

4. The compound according to claim 1, wherein the
pharmaceutically acceptable salt is a salt of an organic acid,
or a substituted derivative thereof, selected from the group
consisting of acetates, propionates, succinates, benzoates,
fumarates, tartrates, theophyllineacetates, salicylates, and
phenolphthalinates.

5. The pharmaceutical composition according to claim 2,
wherein the pharmaceutically acceptable salt is a salt of a
mineral acid, or a substituted derivative thereof, selected
from the group consisting of hydrochlorides, sulfates,
nitrates, and phosphates.

6. The pharmaceutical composition according to claim 2,
wherein the pharmaceutically acceptable salt is a salt of an
organic acid, or a substituted derivative thereof, selected
from the group consisting of acetates, propionates,
succinates, benzoates, fumarates, tartrates,
theophyllineacetates, salicylates, and phenolphthalinates.

7. The pharmaceutical composition according to claim 2,
wherein the therapeutically effective amount of 6-(5-chloro-
2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-
oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, or a pharma-
ceutically acceptable salt thereof, is from about 2.5 mg to
about 15 mg.

8. The pharmaceutically composition according to claim
2, wherein the pharmaceutically acceptable carrier com-
prises a diluent.

* * * * *

EXHIBIT C

(12) **United States Patent**
Cotrel et al.

(10) **Patent No.: US 6,319,926 B1**
(45) **Date of Patent: *Nov. 20, 2001**

- (54) **OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B] PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT**
- (75) Inventors: **Claude Cotrel**, Paris; **G rard Roussel**, Soisy sur Seine, both of (FR)
- (73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)
- (*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

- (21) Appl. No.: **09/124,651**
- (22) Filed: **Jul. 29, 1998**

Related U.S. Application Data

- (63) Continuation of application No. 08/493,946, filed on Jun. 23, 1995, now abandoned, which is a continuation of application No. 08/342,794, filed on Nov. 21, 1994, now abandoned, which is a continuation of application No. 08/232,313, filed on Apr. 25, 1994, now abandoned, which is a continuation of application No. 08/109,863, filed on Aug. 20, 1993, now abandoned, which is a continuation of application No. 08/034,199, filed on Mar. 19, 1993, now abandoned, which is a continuation of application No. 07/821,662, filed on Jan. 16, 1992, now abandoned.

(30) **Foreign Application Priority Data**

- Jan. 17, 1991 (FR) 91 00490
- (51) Int. Cl.⁷ **A61K 31/4985**; C07D 487/04; A61D 25/20
- (52) U.S. Cl. **514/249**; 544/350
- (58) Field of Search 514/249

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,862,149	1/1975	Cotrel et al.	260/268 BQ
4,220,646	9/1980	Cotrel et al.	424/250
4,868,214	9/1989	Sunshine et al.	514/568
4,962,124	10/1990	Sunshine et al.	514/568
5,102,890	4/1992	Bourzat et al.	514/295
5,331,000	7/1994	Young et al.	514/570
5,786,357	7/1998	Young et al.	514/249

FOREIGN PATENT DOCUMENTS

0 495 717	7/1992 (EP) .
WO 93/10788	6/1993 (WO) .

OTHER PUBLICATIONS

Certified Translation of H. Tamura, et al, "Chronic Oral Toxicity Study of Zopiclone (27 267 RP) in Beagle Dogs for 6 Months and Recovery Testing After Treatment," *Pharmacometrics*, 26(6): 969–1003 (1983).

Unpublished summary data sheet from IND Serial No. 000, (s)–zopiclone, owned by assignee Sepracor Inc., p. 8–108 (1 page total) Undated.

Doble et al., "The Pharmacology of Cyclopyrrolone Derivatives Acting at the GABA_A/Benzodiazepine Receptor," *Adv. Biochem. Psychopharmacol.*, 47:407–418 (1992).

Gaillot et al., "Pharmacokinetics and Metabolism of Zopiclone," *Int. Pharmacophysiol.* 17:suppl. 2, pp. 76–91 (1982)/*Pharmacology* 27:suppl. 2, pp. 76–91 (1983).

E.J. Ariens, "Stereoselectivity in Pharmacodynamics and Pharmacokinetics," *Schweiz. Med. Wschr.* 120:131–134 (1990).

Dragstedt, C.A. and Lang, V.F., "Respiratory Stimulants in Acute Cocain Poisoning in Rabbits," *J. Pharmacol. Ex. Ther.* 32:215–222 (1928).

Lichfield, J.T., Jr., and Wilcoxon, F., "A Simplified Method of Evaluating Dose–Effect Experiments," *J. Pharmacol. and Exp. Therap.* 96:99–113 (1949).

Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th ed. (1996) pp. 21–23.

Prieur, David J. et al., "Procedures for Preclinical Toxicology Evaluation of Cancer Chemotherapeutic Agents: Protocols of the Laboratory of Toxicology," *Cancer Chemotherapy Reports*, Jan. 1973, part 3, vol. 4, No. 1:1–30.

Everett et al., "Comparative Anticonvulsive Action of 3,5, 5–Trimethyloxazolidine–2,4–Dione (Tridone), Dilantin and Phenobarbital," *J. Pharmacol.* 81:402 (1944).

Schwinn et al., "Functional Effects of Activation of Alpha–1 Adrenoceptors by Dexmedetomidine: In Vivo and In Vitro Studies," *J. Pharmacol. & Exp. Therap.*, 259 (1991).

Marley et al., "Differential Response to Flurazepan in Long–Sleep and Short–Sleep Mice," *Pharmacol, Biochem. & Behav.*, 31:453–58 (1987).

G. Zbinden et al., "Pharmacology of Benzodiazepines: Laboratory and Clinical Correlations," *Advances in Pharmacology*, 5:213–291 (1967).

W.H. DeCamp, "The FDA Perspective on the Development of Stereoisomers," *Chirality*, 1:2–6 (1989).

D.J. Birkett, "Racemates or Enantiomers: Regulatory Approaches," *Clinical and Experimental Pharmacology & Physiology*, 16:479–483 (1989).

R.F. Squires et al., "Benzodiazepine Receptors in Rat Brain," *Nature*, 266:732–734 (1977).

R.E. Study et al., "Cellular Mechanisms of Benzodiazepine Action," *JAMA*, 247:2147–2151 (1982).

D. Nutt, "Selective Ligands for Benzodiazepine Receptors: Recent Developments," *Curr. Aspects Neurosci.*, 2:259–293 (1990).

(List continued on next page.)

Primary Examiner—Mark Berch
(74) *Attorney, Agent, or Firm*—Sughrue, Mion, Zinn, Macpeak & Seas, PLLC

(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquillizers and hypnotics.

1 Claim, No Drawings

OTHER PUBLICATIONS

- G. Richards et al., "Role of GABA in the mechanism of benzodiazepine action," *Seminars in Neurosciences*, 3:191-203 (1991).
- J.T. Litchfield, "A Method for Rapid Graphic Solution of Time-Percent Effect Curves," *J. Pharmacol. and Exp. Therap.*, 97:399-408 (1949).
- G.W. Snedecor et al., *Statistical Methods*, 7th ed., 149. (No date given).
- Fiche Technique No. 6, *J. Pharmacol. and Experim. Therap.*, 3:407-914 (1970).
- E.J. Ariëns, "Racemic Therapeutics—ethical and regulatory aspects," *Eur. J. Clin. Pharmacol.* 41:89-93 (1991).
- C. Fernandez et al., "Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbonate column," *J. Chromatog.*, 572:195-202 (1991).
- P. Gauthier et al., "Influence of Zopiclone, a New Generation Hypnotic, on the Intermediate Stage and Paradoxical Sleep in the Rat," *Psychopharmacol.*, 130:139-143 (1997).
- Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 8th ed. 346-349 (1990).
- C. Malgouris et al., "Autoradiographic Distribution of [3H]-Suridone Binding Sites in the Rat Brain," *Drug Develop. Res.*, 34:336-343 (1995).
- A. Doble et al., "The mechanism of action of zopiclone," *Eur. Psychiatry*, 10 Suppl. 3:117s-128s (1995).
- J.M. Stutzmann et al., "Pharmacological Properties and Mechanism of Action of the Cyclopyrrolones," *L. Encéphale*, XVIII:393-400 (1992).
- V. Bertolasi et al., "Stereochemistry of Benzodiazepine Receptor Ligands. Possible Role of C-H . . . X Interactions in Drug-Receptor Binding and Crystal Structures of CL 218-872, Zopiclone and DMCM," *J. Chem. Soc. Perkin Trans.*, 2:283-289 (1990).
- F. Jamali et al., "Enantioselective Aspects of Drug Action and Disposition: Therapeutic Pitfalls," *Journal of Pharmaceutical Sciences*, 78(9):695-715 (1989).
- A. Verma and S.H. Snyder, "Peripheral Type Benzodiazepine Receptors," *Annu. Rev. Pharmacol. Toxicol.*, 29:307-322 (1989).
- J.P. Brun, "Zopiclone, a Cyclopyrrolone Hypnotic: Review of Properties," *Pharmacology, Biochemistry and Behavior*, 29:831-832 (1988).
- P.A. Borea et al., "Stereochemical Features Controlling Binding and Intrinsic Activity Properties of Benzodiazepine-Receptor Ligands," *Molecular Pharmacology*, 31:334-344 (1987).
- K.L. Goa and R.C. Heel, "Zopiclone, a Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy as an Hypnotic," *Drugs*, 32(1):48-65 (1986).
- P. Jacqmin and M. Lense, "Les Benzodiazépines: Aspects Pharmacodynamiques," *J. Pharm. Belg.*, 40(1):35-54 (1985).
- L. Julou et al., "Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone," *Pharmacology, Biochemistry and Behavior*, 23:653-659 (1985).
- H. Kusnierczyk, "Antitumor Activity of Optical Isomers of Cyclophosphamide, Ifosfamide and Trofosfamide as Compared to Clinically Used Racemates," *J. Immunopharm.*, 8(4):455-480 (1986).
- F. Jamali, "Pharmacokinetics of enantiomers of chiral non-steroidal anti-inflammatory drugs," *Eur. J. Drug Metab. and Pharmacokin.*, 12(1):1-9 (1988).
- D.W. Robertson et al., "Absolute Configurations and Pharmacological Activities of the Optical Isomers of Fluoxetine & Selective Serotonin-Uptake Inhibitor," *J. Med. Chem.*, 31:1412-1417 (1988).
- Inman W., Kubota K., Pearce G., Wilton W., PEM Report No. 10. Zopiclone, *Pharmacoepidemiol Drug Safety* 1993; 2: 499-521.
- Doble A., Canton T., Malgouris C., et al. The mechanism of action of zopiclone. *Eur Psychiat* 1995; 10 (Suppl 3): 117s-128s.
- Karle J. and Nielsen M., The Mechanism of Action and Pharmacology of Zopiclone, *Rev. Contemp. Pharmacother.*, vol. 9, No. 2, pp. 77-87 (1998).
- Richards G., Schoch P., Haefely W., Benzodiazepine receptors: new vistas. *Sem Neurosci* 1991; 3: 191-203.
- Doble A., Martin I.L., *The GABA₂/benzodiazepine receptor as a target for psychoactive drugs*, RG Landes Company, Austin 1996; pp. 229-264.
- Langtry H.D., Benfield P., Zolpidem: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential, *Drugs*, 1990; 40:291-313.
- Blanchard J.C., Boireau A., Garrett C., Julou L. In vitro and in vivo inhibition by zopiclone of benzodiazepine binding to rodent brain receptors. *Life Sci* 1979; 24: 2417-2420.
- Möhler H., Okada T. The benzodiazepine receptor in normal and pathological human brain. *Brit J Psychiat* 1978; 133: 261-268.
- Gaillot J., Le Roux Y., Houghton G.W., Dreyfus J.F., Critical factors for pharmacokinetics of zopiclone in the elderly and in patients with liver and renal insufficiency. *Sleep* 1987; 10 (Suppl 1): 7-21.
- Braestrup C., Squires R.F., Brain specific benzodiazepine receptors. *Brit J Psychiat* 1978; 133: 249-260.
- Garzone P., Kroboth P., Pharmacokinetics of the Newer Benzodiazepines, *Clinical Pharmacokinetics* 16: 337-364 (1989).
- Miller L.G., Galpern W.R., Brynes J.J., and Greenblatt, D.J., Benzodiazepine Receptor Binding of Benzodiazepine Hypnotics: Receptor and Ligand Specificity, *Pharmacology Biochem. And Beh.* vol. 43, pp. 413-416, 1992.
- Greenblatt D.J., Divoll M., Abernethy D.R., Ochs H.R., and Shader R.I., Clinical Pharmacokinetics of the Newer Benzodiazepines, *Clin Pharmacokinetics*, 8: 233-252 (1983).
- Benavides, J., Peny B., Durand A. et al. Comparative in vivo and in vitro regional selectivity of central ω (benzodiazepine) site ligands in inhibiting [³H]flumazenil binding in the rat central nervous system. *J Pharmacol Exp Therap* 1992; 263: 884-896.
- Ankier S.I., Goa K.L., Quazepam: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Insomnia, *Drugs* 35: 42-62 (1988).
- Gaillot J., Heusse D., Houghton G.W. et al. Pharmacokinetics and metabolism of zopiclone, *Int Pharmacopsychiat* 1983; 17 (Suppl 2): 76-91.
- Nair N.P.V., Schwartz G., Dimitro R. et al. A dose-range finding study of zopiclone in insomniac patients. *Intl Clin Psychopharmacol* 1990; 5 (Suppl 2): 1-10.
- Martindale. The Extra Pharmacopoeia. The Royal Pharmaceutical Society, London 1996; 31st edition: pp. 743-744.

US 6,319,926 B1

Page 3

- Houghton G.W., Dennis M.J., Templeton R., Martin B.K., A repeated dose pharmacokinetic study of a new hypnotic agent, zopiclone (Imovane®). *Intl J Clin Pharmacol Therap Toxicol* 1985; 23: 97–100.
- Marc-Aurèle J., Caille G., Bourgoïn J. Comparison of zopiclone pharmacokinetics in patients with impaired renal function and normal subjects. Effects of hemodialysis. *Sleep* 1987; 10 (Suppl 1): 22–26.
- Parker G., Roberts C.J.C.. Plasmas concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; 16:259–265.
- Viron B., De Meyer M., Le Liboux A. et al., Steady-state pharmacokinetic of zopiclone during multiple oral dosing (7.5 mg nocte) in patients with severe chronic renal failure. *Intl Clin Pysichopharmacol* 1990; 5 (Suppl 2): 95–104.
- Sikdar S., Ruben S.M., Zopiclone abuse among polydrug users. *Addition* 1996; 91: 285–286.
- Noble S., Langtry H.D., Lamb H.M., Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 1998; 55:277–302.
- Fernandez C., Martin C., Gilemenz F., Farinott. Clinical pharmacokinets of zopiclone, *Clin Pharmacokinet* 1995; 29: 431–441.
- Le Liboux Z., Frydman A., Guillot J., Simultaneous Determination of Zopiclone and Its Two Major Metabolites (N–Oxide and N–Desmethyl) in Human Biological Fluids by Reversed–Phase High–Performance Liquid Chromatography, *J. Chromatography*, 417: (1987) 151–158.
- Musch B., and Maillard F., Zopiclone, The Third Generation Hypnotic: a Clinical Overview, *Intl. Clin. Psychopharmacol.* 5: 147–58 (1990).
- Julou L., Blanchard J.C., and Dreyfus J.F., Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone, *Pharmacol., Biochem. & Beh.*, 23: 653–659 (1985).
- Broadhurst A. and Cushnaghan R.C., Residual effects of Zopiclone (Imovane), *Sleep*, 10 (Suppl. 1): 48–53 (1987).
- Anderson A., Zopiclone and Nitrazepam: A Multicenter Placebo Controlled Comparative Study of Efficacy and Tolerance in Insomniac Patient in General Practice, *Sleep*, 10 (Suppl. 1): 54–62 (1987).
- Tamminen T. and Hensen P.P., Chronic Administration of Zopiclone and Nitrazepam in the Treatment of Insomnia, *Sleep*, 10 (Suppl. 1): 63–72 (1987).

US 6,319,926 B1

1

**OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B]
PYRAZINE DERIVATIVE, ITS
PREPARATION AND PHARMACEUTICAL
COMPOSITIONS CONTAINING IT**

This is a continuation of application Ser. No. 08/493,946, filed Jun. 23, 1995, now abandoned, which is a continuation application of Ser. No.: 08/342,794, filed Nov. 21, 1994, now abandoned, which is a continuation application of Ser. No.: 08/232,313, filed Apr. 25, 1994, now abandoned, which is a continuation application of Ser. No.: 08/109,863, filed Aug. 20, 1993, now abandoned, which is a continuation application of Ser. No.: 08/034,199, filed Mar. 19, 1993, now abandoned, which is a continuation application of Ser. No.: 07/821,662, filed Jan. 16, 1992, now abandoned, which are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5 H-pyrrolo [3,4-b] pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5 H-pyrrolo[3,4-b]-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD₅₀) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD₅₀ of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732-734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213-291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

2

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitrites such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnotic, sedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis (β-hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the

US 6,319,926 B1

3

composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46 % yield, a crystallised product (21.3 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}=83^\circ$ C. (c =0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160–165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}=102^\circ$ (c=0.5; acetone), is thereby obtained in a 36 % yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2 N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorota-

4

tory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}=135^\circ\pm3^\circ$ (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}=-21^\circ$ (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2 N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}=-133^\circ\pm3^\circ$ (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

- dextrorotatory isomer of zopiclone . . . 0.003 g
- starch . . . 0.100 g
- precipitated silica . . . 0.035 g
- magnesium stearate . . . 0.005 g

What is claimed is:

1. A method for improving sleep quality or time comprising the step of administering an effective quantity of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl) carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer, to a human.

* * * * *

EXHIBIT D

US007381724B2

(12) **United States Patent**
Cotrel et al.(10) **Patent No.:** **US 7,381,724 B2**
(45) **Date of Patent:** ***Jun. 3, 2008**(54) **OPTICALLY ACTIVE
5H-PYRROLO[3,4-B]PYRAZINE
DERIVATIVE, ITS PREPARATION AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING SAME**(75) Inventors: **Claude Cotrel**, Paris (FR); **Gerard
Roussel**, Soisy sur Seine (FR)(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **11/416,570**(22) Filed: **May 3, 2006**(65) **Prior Publication Data**

US 2006/0194806 A1 Aug. 31, 2006

Related U.S. Application Data(60) Continuation of application No. 10/951,844, filed on
Sep. 28, 2004, now Pat. No. 7,125,874, which is a
continuation of application No. 10/200,510, filed on
Jul. 23, 2002, now Pat. No. 6,864,257, which is a
division of application No. 09/722,438, filed on Nov.
28, 2000, now Pat. No. 6,444,673, which is a con-
tinuation of application No. 09/124,651, filed on Jul.
29, 1998, now Pat. No. 6,319,926, which is a con-
tinuation of application No. 08/493,946, filed on Jun.
23, 1995, now abandoned, which is a continuation of
application No. 08/342,794, filed on Nov. 21, 1994,
now abandoned, which is a continuation of applica-
tion No. 08/232,313, filed on Apr. 25, 1994, now
abandoned, which is a continuation of application No.
08/109,863, filed on Aug. 20, 1993, now abandoned,
which is a continuation of application No. 08/034,
199, filed on Mar. 19, 1993, now abandoned, which is
a continuation of application No. 07/821,662, filed on
Jan. 16, 1992, now abandoned.(30) **Foreign Application Priority Data**

Jan. 17, 1991 (FR) 91 00490

(51) **Int. Cl.****C07D 487/04** (2006.01)**A61K 31/4985** (2006.01)**A61P 25/20** (2006.01)(52) **U.S. Cl.** **514/249; 540/350**(58) **Field of Classification Search** None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

3,862,149 A	1/1975	Cotrel et al.	260/268 BQ
4,220,646 A	9/1980	Cotrel et al.	424/250
4,868,214 A	9/1989	Sunshine et al.	514/568
4,962,124 A	10/1990	Sunshine et al.	514/568
5,102,890 A	4/1992	Bourzat et al.	514/299
5,331,000 A	7/1994	Young et al.	514/570
5,786,357 A	7/1998	Young et al.	
6,319,926 B1	11/2001	Cotrel et al.	
6,436,936 B1	8/2002	Young et al.	
6,444,673 B1	9/2002	Cotrel et al.	
6,864,257 B2	3/2005	Cotrel et al.	
7,125,874 B2	10/2006	Cotrel et al.	
2007/0054914 A1 *	3/2007	Mandava et al.	514/249
2007/0203145 A1 *	8/2007	Zhu	514/249

FOREIGN PATENT DOCUMENTS

EP	0 495 717	7/1992
WO	WO 93/10788	6/1993

OTHER PUBLICATIONS

H. Tamura, et al, "Chronic Oral Toxicity Study of Zopiclone (27 267 RP) in Beagle Dogs for 6 Months and Recovery Testing After Treatment," *Pharmacometrics*, 26(6): 969-1003 (1983).
Unpublished summary data sheet from IND Serial No. 000, (s)-zopiclone, owned by assignee Sepracor Inc., p. 8-108 (1 page total).
Nair N.P.V., Schwartz G., Dimitri R. et al. A dose-range finding study of zopiclone in insomniac patients. *Intl Clin Psychopharmacol* 1990; 5 (Suppl 2): 1-10.
Martindale. The Extra Pharmacopoeia. The Royal Pharmaceutical Society, London 1996; 31st edition; pp. 743-744.
Houghton G.W., Dennis M.J., Templeton R., Martin B.K., A repeated dose pharmacokinetic study of a new hypnotic agent, zopiclone (Imovane®). *Intl J Clin Pharmacol Therap Toxicol* 1985; 23: 97-100.

(Continued)

Primary Examiner—Mark L Berch(74) *Attorney, Agent, or Firm*—Helsin Rothenberg Farley &
Mesiti P.C.(57) **ABSTRACT**

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquilisers and hypnotics.

5 Claims, No Drawings

US 7,381,724 B2

Page 2

OTHER PUBLICATIONS

- Marc-Aurèle J., Caille G., Bourgoïn J. Comparison of zopiclone pharmacokinetics in patients with impaired renal function and normal subjects. Effects of hemodialysis. *Sleep* 1987; 10 (Suppl 1): 22-26.
- Parker G., Roberts C.J.C.. Plasmas concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; 16:259-265.
- Viron B., De Meyer M., Le Liboux A. et al., Steady-state pharmacokinetic of zopiclone during multiple oral dosing (7.5 mg nocte) in patients with severe chronic renal failure. *Intl Clin Psychopharmacol* 1990; 5 (Suppl 2): 95-104.
- Sikdar S., Ruben S.M., Zopiclone abuse among polydrug users. *Addiction* 1996; 91: 285-286.
- Noble S., Langtry H.D., Lamb H.M., Zopiclone. An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 1998; 55:277-302.
- Fernandez C., Martin C., Gimenez F., Farinotti. Clinical pharmacokinetics of zopiclone, *Clin Pharmacokinet* 1995; 29: 431-441.
- Le Liboux Z., Frydman A., Gaillot J., Simultaneous Determination of Zopiclone and its Two Major Metabolites (N-Oxide and N-Désmethyle) in Human Biological Fluids by Reversed-Phase High-Performance Liquid Chromatography, *J. Chromatography*, 417: (1987) 151-158.
- Musch B. and Maillard F., Zopiclone, The Third Generation Hypnotic: a Clinical Overview, *Intl. Clin. Psychopharmacol.* 5: 147-58 (1990).
- Julou L., Blanchard J.C., and Dreyfus J.F., Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone, *Pharmacol., Biochem. & Beh.*, 23: 653-659 (1985).
- Broadhurst A. and Cushnaghan R.C., Residual effects of Zopiclone (Imovane), *Sleep*, 10 (Suppl. 1): 48-53 (1987).
- Anderson A., Zopiclone and Nitrazepam: A Multicenter Placebo Controlled Comparative Study of Efficacy and Tolerance in Insomniac Patients in General Practice, *Sleep*, 10 (Suppl. 1): 54-62 (1987).
- Tamminen T. and Hensen P.P., Chronic Administration of Zopiclone and Nitrazepam in the Treatment of Insomnia, *Sleep*, 10 (Suppl. 1): 63-72 (1987).
- Inman W., Kubota K., Pearce G., Wilton W., PEM Report No. 10. Zopiclone, *Pharmacoepidemiol Drug Safety* 1993; 2: 499-521.
- Doble A., Canton T., Malignous C., et al. The mechanism of action of zopiclone. *Eur Psychiat* 1995; 10 (Suppl 3): 117s-128s.
- Karle J. and Nielsen M., The Mechanism of Action and Pharmacology of Zopiclone, *Rev. Contemp. Pharmacother.*, vol. 9, No. 2, pp. 77-87 (1998).
- Richards G., Schoch P., Haefely W., Benzodiazepine receptors: new vistas. *Sem Neurosci* 1991; 3: 191-203.
- Doble A., Martin I.L., *The GABA_A/benzodiazepine receptor as a target for psychoactive drugs*, RG Landes Company, Austin 1996; pp. 229-264.
- Langtry H.D., Benfield P., Zolpidem: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential, *Drugs*, 1990; 40: 291-313.
- Blanchard J.C., Boireau A., Garret C., Julou L. In vitro and in vivo inhibition by zopiclone of benzodiazepine binding to rodent brain receptors. *Life Sci* 1979; 24: 2417-2420.
- Möhler H., Okada T. The benzodiazepine receptor in normal and pathological human brain. *Brit J Psychiat* 1978; 133: 261-268.
- Gaillot J., Le Roux Y., Houghton G.W., Dreyfus J.F., Critical factors for pharmacokinetics of zopiclone in the elderly and in patients with liver and renal insufficiency. *Sleep* 1987; 10 (Suppl 1): 7-21.
- Doble et al., "The Pharmacology of Cyclopyrrolone Derivatives Acting at the GABA_A/Benzodiazepine Receptor," *Adv. Biochem. Psychopharmacol.*, 47:407-418 (1992).
- Gaillot et al., "Pharmacokinetics and Metabolism of Zopiclone," *Int. Pharmacophysiol.* 17:suppl. 2, pp. 76-91 (1982)/*Pharmacology* 27:suppl. 2, pp. 76-91 (1983).
- E.J. Ariens, "Stereoselectivity in Pharmacodynamics and Pharmacokinetics," *Schweiz. Med. Wschr.* 120:131-134 (1990).
- Dragstedt, C.A. and Lang, V.F., "Respiratory Stimulants in Acute Cocaine Poisoning in Rabbits," *J. Pharmacol. Ex. Ther.* 32:215-222 (1928).
- Litchfield, J.T., Jr., and Wilcoxon, F., "A Simplified Method of Evaluating Dose-Effect Experiments," *J. Pharmacol. and Exp. Therap.* 96:99-113 (1949).
- Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th ed. (1996) pp. 21-23.
- Prieur, David J. et al., "Procedures for Preclinical Toxicologic Evaluation of Cancer Chemotherapeutic Agents: Protocols of the Laboratory of Toxicology," *Cancer Chemotherapy Reports*, Jan. 1973, part 3, vol. 4, No. 1:1-30.
- Everett et al., "Comparative Anticonvulsive Action of 3,5,5-Trimethylxazolidine-2,4-Dione (Tridone), Dilantin and Phenobarbital," *J. Pharmacol.*, 81:402 (1944).
- Schwinn et al., "Functional Effects of Activation of Alpha-1 Adrenoceptors by Dexmedetomidine: In Vivo and In Vitro Studies," *J. Pharmacol. & Exp. Therap.*, 259 (1991).
- Marley et al., "Differential Response to Flurazepam in Long-Sleep and Short-Sleep Mice," *Pharmacol., Biochem. & Behav.*, 31:453-58 (1987).
- G. Zbinden et al., "Pharmacology of Benzodiazepines: Laboratory and Clinical Correlations," *Advances in Pharmacology*, 5:213-291 (1967).
- W.H. DeCamp, "The FDA Perspective on the Development of Stereoisomers," *Chirality*, 1:2-6 (1989).
- D.J. Birkett, "Racemates or Enantiomers: Regulatory Approaches," *Clinical and Experimental Pharmacology & Physiology*, 16:479-483 (1989).
- R.F. Squires et al., "Benzodiazepine Receptors in Rat Brain," *Nature*, 266:732-734 (1977).
- R.E. Study et al., "Cellular Mechanisms of Benzodiazepine Action," *JAMA*, 247:2147-2151 (1982).
- D. Nutt, "Selective Ligands for Benzodiazepine Receptors: Recent Developments," *Curr. Aspects Neurosci.*, 2:259-293 (1990).
- G. Richards et al., "Role of GABA in the mechanism of benzodiazepine action," *Seminars in Neurosciences*, 3:191-203 (1991).
- J.T. Litchfield, "A Method for Rapid Graphic Solution of Time-Percent Effect Curves," *J. Pharmacol. and Exp. Therap.*, 97:399-408 (1949).
- G.W. Snedecor et al., Statistical Methods, 7th ed., 149.
- Fiche Technique No. 6, J. Pharmacol. and Experim. Therap., 3:407-914 (1970).
- E.J. Ariens, "Racemic Therapeutics—ethical and regulatory aspects," *Eur. J. Clin. Pharmacol.* 41:89-93 (1991).
- C. Fernandez et al., "Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbonate column," *J. Chromatog.*, 572:195-202 (1991).
- P. Gauthier et al., "Influence of Zopiclone, a New Generation Hypnotic, on the Intermediate Stage and Paradoxical Sleep in the Rat," *Psychopharmacol.*, 130:139-143 (1997).
- Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 8th ed. 346-349 (1990).
- C. Malignous et al., "Autoradiographic Distribution of [3H]-Suridone Binding Sites in the Rat Brain," *Drug Develop. Res.*, 34:336-343 (1995).
- A. Doble et al., "The mechanism of action of zopiclone," *Eur. Psychiatry*, 10 Suppl. 3:117s-128s (1995).
- J.M. Stutzmann et al., "Pharmacological Properties and Mechanism of Action of the Cyclopyrrolones," *L. Encéphale*, XVIII:393-400 (1992).
- V. Bertolasi et al., "Stereochemistry of Benzodiazepine Receptor Ligands. Possible Role of C-H...X Interactions in Drug-Receptor Binding and Crystal Structures of CL 218-872, Zopiclone and DMCM," *J. Chem. Soc. Perkin Trans.*, 2:283-289 (1990).
- F. Jamali et al., "Enantioselective Aspects of Drug Action and Disposition: Therapeutic Pitfalls," *Journal of Pharmaceutical Sciences*, 78(9):695-715 (1989).
- A. Verma and S.H. Snyder, "Peripheral Type Benzodiazepine Receptors," *Annu. Rev. Pharmacol. Toxicol.*, 29:307-322 (1989).

US 7,381,724 B2

Page 3

- J.P. Brun, "Zopiclone, a Cyclopyrrolone Hypnotic: Review of Properties," *Pharmacology, Biochemistry and Behavior*, 29:831-832 (1988).
- P.A. Borea et al., "Stereochemical Features Controlling Binding and Intrinsic Activity Properties of Benzodiazepine-Receptor Ligands", *Molecular Pharmacology*, 31:334-344 (1987).
- K.L. Goa and R.C. Heel, "Zopiclone, a Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy as an Hypnotic," *Drugs*, 32(1):48-65 (1986).
- P. Jacqmin and M. Lesne, "Les Benzodiazepines: Aspects Pharmacodynamiques," *J. Pharm. Belg.*, 40(1):35-54 (1985).
- L. Julou et al., "Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone," *Pharmacology, Biochemistry and Behavior*, 23:653-659 (1985).
- H. Kusnierczyk, "Antitumor Activity of Optical Isomers of Cyclophosphamide, Ifosfamide and Trofosfamide as Compared to Clinically Used Racemates," *J. Immunopharm.*, 8(4):455-480 (1986).
- F. Jamali, "Pharmacokinetics of enantiomers of chiral non-steroidal anti-inflammatory drugs," *Eur. J. Drug Metab. and Pharmacokin.*, 12(1):1-9 (1988).
- D.W. Robertson et al., "Absolute Configurations and Pharmacological Activities of the Optical Isomers of Fluoxetine & Selective Serotonin-Uptake Inhibitor," *J. Med. Chem.*, 31:1412-1417 (1988).
- Braestrup C., Squires R.F., Brain specific benzodiazepine receptors. *Brit J Psychiat* 1978; 133: 249-260.
- Garzone P., Kroboth P., Pharmacokinetics of the Newer Benzodiazepines, *Clinical Pharmacokinetics* 16: 337-364 (1989).
- Miller L.G., Galpern W.R., Byrnes J.J., and Greenblatt, D.J., Benzodiazepine Receptor Binding of Benzodiazepine Hypnotics: Receptor and Ligand Specificity, *Pharmacology Biochem. And Beh.* vol. 43, pp. 413-416, 1992.
- Greenblatt D.J., Divoll M., Abernethy D.R., Ochs H.R., and Shader R.I., Clinical Pharmacokinetics of the Newer Benzodiazepines, *Clin Pharmacokinetics*, 8: 233-252 (1983).
- Benavides, J., Peny B., Durand A. et al. Comparative in vivo and in vitro regional selectivity of central ω (benzodiazepine) site ligands in inhibiting [3 H]flumazenil binding in the rat central nervous system. *J Pharmacol Exp Therap* 1992; 263: 884-896.
- Ankier S.I., Goa K.L., Quazepam: A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Insomnia, *Drugs* 35: 42-62 (1988).
- Gaillot J., Heusse D., Houghton G.W. et al. Pharmacokinetics and metabolism of zopiclone. *Int Pharmacopsychiat* 1983; 17 (Suppl 2): 76-91.
- 8th European Crystallographic Meeting, 1983 Abstract 1.19P, Bertolasi et al., "Stereochemistry of Benzodiazepine-Receptor Ligands. The Molecular Structure of Zopiclone," 32 (1983).
- Shankland et al. "Structural transformations in zopiclone" Chem. Commun. 2204-2205 (2001).
- Terblanche et al. "Characterization of Zopiclone Crystal Forms Found Among Generic Raw Materials" Drug Dev. and Indus. Pharm. 26(5), 531-537 (2000).
- Giovannini et al. "Polymorphism and hydration of zopiclone: Determination of crystal structures and, thermodynamic studies as a function of temperature and water vapor pressure" J. Phys. IV France 11(Pr10), 93-97 (Dec. 2001).
- Jacqmin et al. Selective Affinity of one Enantiomer of Suriclone Demonstrated by a Binding Assay with Benzodiazepine Receptors. Arch. int. Pharmacodyn. 282, 26-32 (1986).
- Codding, P. et al. Structure of Suriclone, a Benzodiazepine Receptor Agonist. Acta Cryst. C44, 1938-1942 (1988).

* cited by examiner

US 7,381,724 B2

1

**OPTICALLY ACTIVE
5H-PYRROLO[3,4-B]PYRAZINE
DERIVATIVE, ITS PREPARATION AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING SAME**

CROSS REFERENCE TO RELATED
APPLICATIONS

This application is a continuation of application Ser. No. 10/951,844, filed Sep. 28, 2004, now U.S. Pat. No. 7,125,874, which is a continuation of application Ser. No. 10/200,510, filed Jul. 23, 2002, now U.S. Pat. No. 6,864,257, which is a divisional of application Ser. No. 09/722,438, filed Nov. 28, 2000, now U.S. Pat. No. 6,444,673, which is a continuation of application Ser. No. 09/124,651, filed Jul. 29, 1998, now U.S. Pat. No. 6,319,926, which is a continuation of application Ser. No. 08/493,946, filed Jun. 23, 1995 (abandoned), which is a continuation of application Ser. No. 08/342,794, filed Nov. 21, 1994 (abandoned), which is a continuation of application Ser. No. 08/232,313, filed Apr. 25, 1994 (abandoned), which is a continuation of application Ser. No. 08/109,863, filed Aug. 20, 1993 (abandoned), which is a continuation of application Ser. No. 08/034,199, filed Mar. 19, 1993 (abandoned), which is a continuation of application Ser. No. 07/821,662, filed Jan. 16, 1992 (abandoned). U.S. Ser. No. 07/821,662 claimed the priority of French application 91 00490, filed Jan. 17, 1991. The entire contents of each of the prior applications are incorporated herein by reference.

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo[3,4-b]pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD₅₀) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD₅₀ of between 300 and 900 mg/kg.

2

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J. C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732-734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213-291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitrites such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis (β -hydroxynaphthoates), or of substitution derivatives of these acids, may be mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or

US 7,381,724 B2

3

starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46% yield, a crystallised product (21.3 g), m.p. 160-165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}=83^\circ$ (c=0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5° C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160-165° C. (with decomposition), the optical rotation of which is $[\alpha]_D^{20}=102^\circ$ (c=0.5; acetone), is thereby obtained in a 36% yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the

4

product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5° C., the optical rotation of which is $[\alpha]_D^{20}=135^\circ\pm 3^\circ$ (c=1.0; acetone), is obtained in a 23% yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20}=-21^\circ$ (c=0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9° C., the optical rotation of which is $[\alpha]_D^{20}=-133^\circ\pm 3^\circ$ (c=1.0; acetone), is thereby obtained in a 13.9% yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

dextrorotatory isomer of zopiclone	0.003 g
starch	0.100 g
precipitated silica	0.035 g
magnesium stearate	0.005 g

The invention claimed is:

1. A mixture of isomers of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyl-oxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, wherein the mixture has an optical rotation $[\alpha]_D^{20}$ of $135^\circ\pm 3^\circ$ when measured at 1.0 g/100 mL in acetone.

2. A pharmaceutical composition comprising the mixture of claim 1 and one or more pharmaceutically acceptable diluents, coatings, lubricants, wetting products, sweetening products, flavouring products, solvents, vehicles or adjuvants.

3. The pharmaceutical composition of claim 2 that is in the form of a tablet, pill, powder or granule.

4. The pharmaceutical composition of claim 2 that is in the form of a tablet.

5. A method of inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquilizing effect, comprising administering to a human in need thereof an effective amount of the mixture of claim 1.

* * * * *